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CHANGES IN FATTY ACID COMPOSITION AND RATIO IN RAT BRAIN LIPIDES AS A PREDICTOR OF THE DEVELOPMENT OF ALLERGENIC NEUROPATHY UNDER COMBINED ACTION OF POLYMERIC MATERIALS COMPONENTS

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Abstract

Background. The nervous system failures are caused by the influence of various harmful industrial and environmental factors. Among them polymers play an important role. Polymeric materials (PM) and additive substances can be sources of significant disorders in the lipid metabolism, changes in fatty acid composition and ratio, neurotoxic effects development. But till now many aspects of such disorders mechanisms and interrelations remains unclear.

Purpose. This study aimed at determining the changes in the fatty acid composition, ratio and metabolism in the brain tissues under the action of PM components combination (in particular, cadmium (Cd) and dibutyl phthalate (DBP)), to assess at the experimental model of sensitization the importance of this mechanism and show the ability to use it as an informative marker in the hygienic certification of PM.

Materials and methods. The experiment was conducted on 48 white male rats of the Wistar line weighing 180-200 g. All animals divided in 4 groups: individual and combined exposure of $CdCl_2$ and DBP with Friend's complete adjuvant (FCA) adding and control group. The studies were performed in accordance with adaptation phases in two stages: at 33d

and 72d days of chemicals administration. Complex of biomarkers were used: behavioral reactions – with the set-shifting tests "Cross maze" (CM) and "Open field" (OF); sensitization - by the reaction of specific leukocyte agglomeration (RSAL), fatty acids content – by modified Folch's method and gas chromatography. Data processing was performed using common statistical parametric and non-parametric methods.

Results. On the 33rd day of the experiment in animals the 2nd (DBP) and the 4th (DBP + $CdCl_2$), the reaction of the leukocytes specific agglomeration (RLSA) index was 1.93 ± 0.12 points ($p < 0.01$), in 4 th - 2.06 ± 0.15 points ($p < 0.001$), respectively, which is a sign of the development of an allergic reaction by the delayed-type of hypersensitivity. These changes were sustainable, remaining until the end of the experiment ($p < 0.01$ for 72 days). The assessment of the nervous system functional activity in dynamics of the experiment revealed the earliest changes in motility in animals of the 4th group in terms of the total number of visits to the deadlocks in the CM test - a decrease of more than 2.5 times compared to the control and background indicators. Multidirectional changes were also found in the ratio of mono- / polyunsaturated fatty acids in all groups: in the 2nd and 4th the coefficient decreased by 1.43 and 1.9 times, and in the 3rd - increased by 1.3 times. The polyunsaturated FA ratio in the brain lipids of the 2nd and 4th groups also revealed a number of changes: a decrease in the total content of ω 3 unsaturated FA (USFA) and an increase in ω 6 USFA with a corresponding change in ω6 / ω3 - an increase of 3.2 and 4,2 times, respectively, in relation to the control. These disorders may play an important role in the development of cognitive disorders and neurodegenerative diseases a disregulatory nature with the combined action of the components of the PM.

Conclusions. Research results are showed that an experimental model of delayed-type hypersensitivity, accompanied by changes in the spectrum and ratio of fatty acids in rat brain tissues, can be used as a complex of informative biomarkers in the process of hygienic certification of PM, studying the pathogenic mechanisms of neurotoxicity and searching for effective ways and means of protection.

Kaywords: polymeric materials, volatile components, neurotoxicity, immune-alergic action, markers, fatty acids, hygienic sertification

ИЗМЕНЕНИЯ СОСТАВА И СООТНОШЕНИЯ ЖИРНЫХ КИСЛОТ В ЛИПИДАХ МОЗГА КРЫСЫ КАК ПРЕДИКТОРЫ РАЗВИТИЯ АЛЛЕРГЕННОЙ НЕЙРОПАТИИ ПРИ КОМБИНИРОВАННОМ ДЕЙСТВИИ КОМПОНЕНТОВ ПОЛИМЕРНЫХ МАТЕРИАЛОВ

Е. В. Третьякова

Реферат

Обоснование. Нарушения нервной системы могут быть вызваны влиянием различных вредных производственных и экологических факторов. Среди них важную роль играют полимеры. Полимерные материалы (ПМ) и аддитивные вещества могут быть источниками значительных нарушений метаболизма липидов, изменений в составе и соотношении жирных кислот, развития нейротоксических эффектов. Но до сих пор многие аспекты механизмов и взаимосвязей таких нарушений остаются неясными.

Цель. Это исследование было направлено на определение на экспериментальной модели гиперчувствительности замедленного типа изменений в составе, соотношении и метаболизме жирных кислот в тканях головного мозга крыс под действием комбинации компонентов ПМ (в частности, кадмия (Cd) и дибутилфталата (DBP)) для оценки участия этого механизма в токсическом действии факторов малой интенсивности и возможности использованич его в качестве информативного маркера в гигиенической сертификации РМ.

Материалы и методы. Эксперимент проведен на 48 белых самцах крыс линии Вистар массой 180-200 г. Все животные были разделены на 4 группы: индивидуальное и комбинированное воздействие CdCl2 и DBP с добавлением и полным контролем адъюванта (FCA) Френда. Исследования проводились в соответствии с фазами адаптации в два этапа: через 33 дня и через 72 дня после введения химикатов. Использовали комплекс биомаркеров: поведенческие реакции - с помощью сдвиговых тестов «Крестный лабиринт» (СМ) и «Открытое поле» (ОФ); сенсибилизация - реакцией специфической агломерации лейкоцитов (RSAL), содержания жирных кислот - модифицированным методом Фольча и газовой хроматографией. Обработка данных проводилась с использованием общих статистических параметрических и непараметрических методов.

Результаты. На 33-й день эксперимента у животных 2-й (ДАД) и 4-й (ДАД + CdCl2) реакция индекса специфической агломерации лейкоцитов (RLSA) составила 1,93 ± 0,12 балла (p <0,01), у 4-го - 2,06 ± 0,15 балла (p <0,001) соответственно, что является признаком развития аллергической реакции гиперчувствительности замедленного типа. Эти изменения были устойчивыми, сохраняющимися до конца эксперимента (p <0,01 в течение 72 дней). Оценка функциональной активности нервной системы в динамике эксперимента позволила выявить наиболее ранние изменения моторики у животных 4-й группы по общему количеству посещений тупиков в тесте СМ - снижение более чем в 2,5 раза по сравнению с контрольные и фоновые показатели. Разнонаправленные изменения были обнаружены и в соотношении моно- / полиненасыщенных жирных кислот во всех группах: во 2-й и 4-й коэффициент уменьшился в 1,43 и 1,9 раза, а в 3-й - увеличился в 1,3 раза. Отношение полиненасыщенных ЖК в липидах мозга 2-й и 4-й групп также выявило ряд изменений: уменьшение общего содержания ω 3-ненасыщенных ЖК (USFA) и увеличение ω 6 USFA с соответствующим изменением ω6 / ω3 - увеличение в 3,2 и 4,2 раза соответственно по отношению к контролю. Эти нарушения могут играть важную роль в развитии когнитивных расстройств и нейродегенеративных заболеваний дизрегуляторного характера при комбинированном действии компонентов ПМ.

Выводы. Результаты исследований показывают, что экспериментальная модель гиперчувствительности замедленного типа, сопровождающаяся изменениями спектра и соотношения жирных кислот в тканях мозга крыс, может быть использована в качестве комплекса информативных биомаркеров в процессе гигиенической сертификации ПМ, изучения патогенных механизмов нейротоксичности и в поисках эффективных способов и средств защиты.

Ключевые слова: **полимерные материалы, летучие компоненты, нейротоксичность, иммуно-аллергическое действие, маркеры, жирные кислоты, гигиеническая регуляция**

ZMIANY SKŁADU I SKŁADU KWASU TŁUSZCZOWEGO W LIPIDACH MÓZGOWYCH JAKO PRZEDSTAWICIELSTWO ROZWOJU ALERGENNY NEUROPATHY W RAMACH POŁĄCZONYCH DZIAŁAŃ KOMPONENTÓW MATERIAŁÓW POLIMEROWYCH

E. V. Tretyakova

Podsumowanie

Uzasadnienie. Naruszenie układu nerwowego może być spowodowane wpływem różnych szkodliwych czynników przemysłowych i środowiskowych. Wśród nich ważną rolę odgrywają polimery. Materiały polimerowe (PM) i substancje dodatkowe mogą być źródłem istotnych zaburzeń metabolizmu lipidów, zmian w składzie i stosunku kwasów tłuszczowych, rozwoju efektów neurotoksycznych. Ale jak dotąd wiele aspektów mechanizmów i powiązań takich naruszeń pozostaje niejasnych.

Cel. Celem tego badania było określenie, w modelu doświadczalnym nadwrażliwości typu opóźnionego, zmian w składzie, proporcji i metabolizmie kwasów tłuszczowych w tkankach mózgu szczura pod wpływem połączenia składników PM (w szczególności kadmu (Cd) i ftalanu dibutylu (DBP)) w celu oceny zaangażowania tego mechanizmu w toksycznych skutkach czynników o niskiej intensywności i możliwości wykorzystania go jako markera informacyjnego w certyfikacji higienicznej PM.

Materiały i metody. Eksperyment przeprowadzono na 48 białych samcach szczurów Wistar o wadze 180-200 g. Wszystkie zwierzęta podzielono na 4 grupy: indywidualne i połączone efekty CdCl2 i DBP z dodatkiem i pełną kontrolą Adjuvant (FCA) Friend. Badania zostały przeprowadzone zgodnie z fazami adaptacyjnymi w dwóch etapach: 33 dni później i 72 dni po wprowadzeniu chemikaliów. Zastosowano kompleks biomarkerów: reakcje behawioralne - za pomocą testów ścinania "OF Lab" (SM) i "Open Field" (OF); uczulenie - przez reakcję specyficznej aglomeracji leukocytów (RSAL), zawartość kwasów tłuszczowych - zmodyfikowaną metodą Folcha i chromatografią gazową. Przetwarzanie danych przeprowadzono za pomocą ogólnych statystycznych metod parametrycznych i nieparametrycznych.

Wyniki. W 33 dniu doświadczenia, 2 zwierzęta (DAP) i 4 zwierzęta (DAD + CdCl2) wykazywały reakcję określonego wskaźnika aglomeracji leukocytów (RLSA) 1,93 ± 0,12 punktu ($p < 0,01$), w 4 th - 2,06 ± 0,15 punktu ($p < 0,001$), co jest oznaką rozwoju reakcji alergicznej typu nadwrażliwości typu opóźnionego. Zmiany te były stabilne i utrzymywały się

do końca eksperymentu (p <0,01 przez 72 dni). Ocena funkcjonalnej aktywności układu nerwowego w dynamice eksperymentu ujawniła najwcześniejsze zmiany w ruchliwości zwierząt czwartej grupy, zgodnie z całkowitą liczbą wizyt w ślepych zaułkach w teście CM - spadek o ponad 2,5 razy w porównaniu ze wskaźnikami kontrolnymi i tła. Wielokierunkowe zmiany stwierdzono w stosunku do mono- / wielonienasyconych kwasów tłuszczowych we wszystkich grupach: w 2 i 4, stosunek zmniejszył się o 1,43 i 1,9 razy, aw trzecim - wzrósł o 1,3 razy. Stosunek wielonienasyconych kwasów tłuszczowych w lipidach mózgu 2. i 4. grupy ujawnił także szereg zmian: zmniejszenie całkowitej zawartości ω-nienasyconych kwasów tłuszczowych (USFA) i wzrost ω 6 USFA z odpowiednią zmianą w ω6 / ω3 - wzrost o 3,2 i 4, 2 razy odpowiednio w stosunku do kontroli. Zaburzenia te mogą odgrywać ważną rolę w rozwoju zaburzeń poznawczych i chorób neurodegeneracyjnych o charakterze dysregulacyjnym z połączonym działaniem składników PM.

Wnioski. Wyniki badań pokazują, że eksperymentalny model nadwrażliwości typu opóźnionego, któremu towarzyszą zmiany w spektrum i stosunku kwasów tłuszczowych w tkankach mózgu szczura, można wykorzystać jako zespół biomarkerów informacyjnych w procesie certyfikacji higienicznej PM, badania patogennych mechanizmów neurotoksyczności oraz poszukiwania skutecznych sposobów i środków ochrony.

Słowa kluczowe: materiały polimerowe, składniki lotne, neurotoksyczność, działanie immunoalergiczne, markery, kwasy tłuszczowe, regulacja higieniczna

Introduction. The functional changes and pathological effects in the nervous system caused by the influence of various harmful industrial and environmental factors is an actual problem for both clinical and prophylactic direction of medical science [1, 2]. A significant amount of data has been accumulated on the development of neurotoxic effects under the exposition of chemicals, noise and vibration, radiation, the immunological status violation with infectious agents, etc. [3-5]. An important feature of the nervous system functions and structure pathological changes are the lipid metabolism disorders and, particular, fatty acids ratio [6]. Therefore, in the development of neurotoxic effects, an important role can be play the fatty acid disorders as informative patterns of chemical etiology neurotoxicogenesis [7].

Of great interest in this regard are polymeric materials (PM) and additive substances included in their formulation, which can cause essential in various tissues. During operation, PM and their products are the sources of migration into the air of industrial, residential and transport facilities with permanent and constant presence of people wide range of low

molecular weight chemicals and compounds in relatively low concentrations. However, with prolonged contact, these components of PM may initiate the development of neurotoxic, neuroendocrine, vascular, allergenic (like a delayed type of hypersensitivity (GST)) and other pathological processes that differ in pathogenesis from classical (traditional) acute and chronic poisonings with intense exposure levels [9, 10].

However, the study of biochemical mechanisms and patterns of lipid metabolism disorders in nervous tissue, its role in the development of pathological processes of neuroallergic genesis, especially under the combined action of PM components with different types of specific action, remains relevant.

The purpose of the study was to use a combination of chemicals, common components of PM (in particular, cadmium (Cd) and dibutyl phthalate (DBP)), to assess the changes in the fatty acid composition, ratio and metabolism in the brain tissues on the experimental model of sensitization; to substantiate the possibility of using this indicator as an informative biomarker the nervous system pathological changes and and show the ability to use it as an informative biomarker in the system of PM hygienic standartzation.

Materials and methods. The studies were conducted on 48 white male rats of the Wistar line weighing 180-200 g in compliance with the requirements of bioethics, which are corresponds with the provisions of the European Convention for the vertebrate animals protection in experimental researches [11].

Animals were divided into 4 groups, each of 12 rats. At the stage of preparation of the experiment to assess the effects of chemicals on the central nervous system, individual-typological behavior features of animal were measured and groups were formed according to body mass index and types of higher nervous system activity (HNA). The studies were performed on the background of a simulation of animal sensitization to the studied components of PM, using the standard scheme of allergyzation with Freund's complete adjuvant (FCA) [12]. To do this, animals of all groups were previously subcutaneously injected with 0.2 ml of FCA in 0.2 ml of 0.9% NaCl solution, and after 3 days, animals of the 1st group received 0.2 ml of FCA in 0.2 ml of 0.9% NaCl (control); 2nd group – DBP at a dose of 1/100 from DL50 v / b (5.0 mg / kg) + FCA, 3rd - $CdCl_2$ at a dose of 1/100 from DL50 v / b (0.3 mg / kg per) + FCA and 4th - combination of DBP + $CdCl_2$ + PAF in the same way. On the 10th day of the experiment provocation was carried out by administering half the doses of the toxicants according to the same scheme.

The studies were performed in two stages, taking into account the completion of the primary phases of the adaptation process [13]: 1. On the 33rd day of the experiment, the

animals of all groups determined the indicators of the organism immune-allergic reorganization by the reaction of specific leukocyte agglomeration (RSAL), as well as the number and ratio of the main types of leukocytes in peripheral blood of animals [14]. 2. On the 72nd day of experiment, animals were decapitated after preliminary anesthesia (Aldrich firm 2.5% 2,2,2-tribromomethanol in 2-methylbutanol; 1:50 in PBS; 300 mg / kg intraperitoneal injection).

To assess the behavioral reactions of animals, that characterize the CNS functional state, the set-shifting tests "Cross maze" (CM) and "Open field" (OF) were successively performed (by increasing the stress effect). These methods and the characteristics of behavioral patterns are described in more detail in [15], previously published by the author of this work. Animals were examined before the start of the experiment ("background indicators"), in the dynamics of the experiment (4 and 8 weeks), and a separate group after the end of the recovery period (on the 12th week).

After the animals were removed from the experiment (72d day), in brain tissue the spectrum and the ratio of fatty acids (FA) were determined. Extraction of lipids from the tissues was carried out according to the method of Bligh and Dayer (a modified method of Folch). [15, 16]. The resulting LCs were converted to methyl esters, followed by chromatographic separation on a Crystallux-4000 gas chromatograph with a flame ionization detector on a Zebron ZB-WAX 60 m L x 0.53 mm ID x 1.0 μm df capillary column. Programmable temperature mode - from 140 to 260 OS. LCD peaks were identified by comparison with standard samples (Sigma-Aldrig, USA). The quantitative content of FA was estimated by the peak area and was calculated by the percentage normalization method.

Statistical processing of the results was performed using the standard software package in Microsoft Excel [17].

The results of the study. When examined on the 33rd day of the experiment in animals the 2nd (DBP + FCA) and the 4th (DBP + $CdCl_2$ + FCA), the RSAL index was 1.93 ± 0.12 points ($p < 0.01$), in 4 th - 2.06 ± 0.15 points ($p < 0.001$), respectively, which is a sign of the development of an allergic reaction by the delayed-type of hypersensitivity. These changes were sustainable, remaining until the end of the experiment ($p < 0.01$ for 72 days). In the control and the 3rd group ($CdCl_2$ + FCA) the level of RSAL practically did not change (no more than 1.27 points). The results obtained and their interpretation are described in more detail in previous publications on this series of experiments [8]. The assessment of the of the nervous system functional activity in dynamics of the experiment revealed the earliest changes in motility in animals of the 4th group in terms of the total number of visits to the

deadlocks in the CM test - a decrease of more than 2.5 times compared to the control and background indicators (Fig. 1)

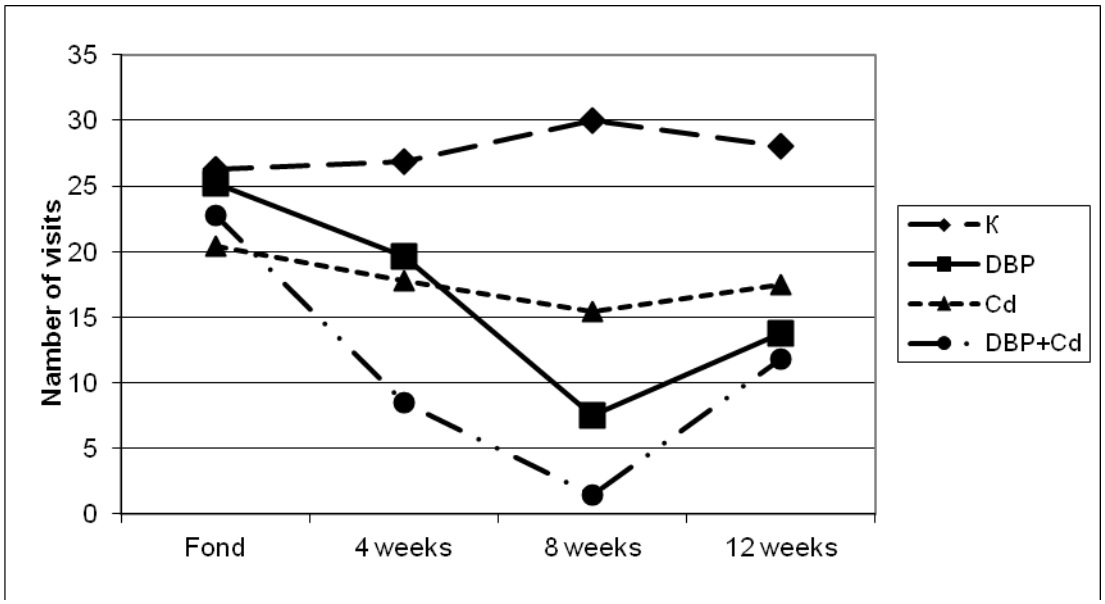

Fig. 1. The total number of visit dynamics to the deadlocks in the CM test

To the end of experiment, this marker was significantly lower than the background values in the 2nd and 4th groups - by 70.0 and 93.4 % ($p < 0.01$). By the end of the recovery period, indicators did not restored to the level of background values. On the 4th week of the experiment, changes in the level of motor and orientative-exploratory activity of animals in the OF test were also detected in the 2nd and 4th groups - a decrease in horizontal motor activity by more than 2.5 times, and vertical - in 2 times ($p < 0.05$). In the emotional and cognitive sphere of animals in the 2nd and 4th groups at the peak of delayed hyperactivity development (4 weeks), an increase in the time of the latent period (in CM test) was revealed by more than 2 times, anxiety increase (increased grooming) by 4 weeks and decrease by more than 2 times by the end of the experiment ($p < 0.05$). By the end of the recovery period, the indicators did not reach the levels of background values This indicated the depletion of the adaptative and compensatory reservs.

In the FA spectrum of lipid extracts in animal brain tissue, 27 of the most biologically significant FAs have been identified. the table. 1 As can be seen from the received data, marked multidirectional changes in the ratio of individual FA fractions in different experimental groups were indicated by the end of the experiment.

Table 1

The content of the FA in the brain tissues of experimental animals after the end of the chronic experiment

№ п/п	Marker	Grops of animal, FA content			
		Control	DBP+FCA	$CdCl_2$+FCA	DBP+$CdCl_2$+ FCA
1	2	3	4	5	6
1	Myristic, C 14:0	0,12±0,011	**0,32±0,04*** **	0,12±0,01	**0,74±0,08*** **
2	Myristoleic, C 14:1	0,06±0,05	**0,6±0,07*** **	0,11±0,01	**0,33±0,04*** **
3	Methylpentadecane, C 15:0	0,8±0,09	**0,38±0,04** **	**2,44±0,27*** **	**0,26±0,03*** **
4	Cis-10-pentadecane, C 15:1	0,91±0,11	**0,57±0,06***	0,74±0,08	0,88±0,09
5	Palmitic, C 16:0	18,2±2,08	18,4±1,9	19,42±2,2	19,5±2,2
6	Palmito-oleic, C 16:1 п 7	0,81±0,09	**0,42±0,05** **	**3,92±0,43*** **	**0,54±0,06** **
7	Margarine, C 17:0	0,81±0,07	0,65±0,07	**0,27±0,03*** **	**0,32±0,04*** **
8	Cis-10-heptatadec, C 17:1	1,68±0,19	**0,75±0,09** **	2,14±0,29	**0,66±0,07*** **
9	Stearic, C 18:0	18,1±2,1	23,3±2,5	15,78±1,7	**27,2±2,9***
10	Oleic , C 18:1 ω 9	25,2±2,7	23,6±2,6	26,8±2,7	20,6±2,1
11	Linolic C 18:2 ω 6	1,99±0,22	1,87±0,20	2,05±0,21	1,79±0,18
12	γ-Linolenic C 18:3 ω 6	0,11±0,01	0,09±0,01	**0,04±0,005** **	-
13	α-Linolenic C 18:3 ω 3	0,18±0,02	0,14±0,01	0,19±0,02	**0,13±0,01***
14	Arachidic, C 20:0	0,36±0,04	0,38±0,04	0,29±0,03	**0,26±0,03** **
15	Gondoinic, C 20:1 ω 9	4,5±0,49	3,13±0,36	**1,96±0,22*** **	**1,08±0,13*** **
16	Eicosadienic, C 20:2 ω 6	0,15±0,02	**0,44±0,05*** **	0,07±0,009	-
17	Digomo-γ-linolenic,C 20:3 ω 6	0,52±0,06	**1,62±0,19*** **	0,68±0,073	**2,12±0,26*** **
18	Eicosatrienic, C 20:3 ω 3	0,05±0,007	-	**0,03±0,004**	-
19	Arachidonic, C 20:4 ω 6	5,2±0,06	**8,13±0,92**	4,62±0,49	**9,79±0,99**
20	Eicosapentaenic, C 20:5 ω 3	0,12±0,01	-	**0,05±0,006**	-
21	Behenic, C 22:0	1,01±0,11	**0,08±0,01*** **	**0,13±0,01** **	-
22	Erucic, C 22:1 ω 9	0,15±0,02	-	**0,09±0,011**	-

1	2	3	4	5	6
23	Docosadienic, C 22:2 ω 6	0,12±0,01	0,13±0,01	0,1±0,01	0,16±0,02
24	Docosatetraenic, C 22:4 ω 6	2,24±0,03	2,98±0,34	2,04±0,24	**3,38±0,38****
25	Docosapentaenoic, C 22:5 ω 3	0,81±0,09	**0,53±0,06***	0,79±0,08	**0,4±0,05****
26	Docosahexaenoic, C 22:6 ω 3	5,35±0,62	4,05±0,49	5,39±0,55	**3,6±0,38***
27	Nervonic, C 24:1 ω 9	10,5±1,12	**7,4±0,83***	9,4±0,97	**5,9±0,62****
The sum of all FA		99,99	99,96	99,67	99,66
The all saturated FA amount		39,4	43,51	38,45	48,28
The unsaturated FA amount		60,59	56,45	61,22	51,38
The saturated / unsaturated FA ratio		0,65	0,77	0,63	0,94
The monounsaturated FA amount		43,75	36,47	47,17	29,99
The polyunsaturated FA amount		16,84	19,98	14,05	21,39
The ratio of mono- / polyunsaturated FA		2,6	1,82	3,35	1,4

Notes: */ - p<0,05; **/ - p<0,01***/ - p<0,001

Significant changes in the ratio of saturated / unsaturated fatty acids were detected in the 4th group, mainly due to increase in the relative content of stearic FA (in more than 1.5 times). Long-chain saturated FAs are the main structural components of cell membranes, and their packing density showed growing increase. At the same time, in this group there was a significant decreased the total amount of unsaturated FAs (in 1.17) times and the ratio of saturated / unsaturated FAs (by more than 1.4 times). All this may indicate a disturbance of metabolic processes presence and lead to a decrease in the excitability of neuronal synapses.

Multidirectional changes were also found in the ratio of mono- / polyunsaturated fatty acids in all experimental groups — in the 2nd and 4th, the coefficient decreased by 1.43 and 1.9 times, and in the 3rd - increased by 1.3 times. The reduction of monoenic FA occurs mainly due to ω-9 components, which are interchangeable and are involved in the antioxidant defense process.

The polyunsaturated FA ratio in the brain lipids of the 2nd and 4th groups also revealed a number of changes: a decrease in the total content of ω 3 unsaturated FA (USFA) and an increase in ω 6 USFA with a corresponding change in ω6 / ω3 - an increase of 3.2 and

4 , 2 times, respectively, in relation to the control. At the same time, the relative amount of irreplaceable α-Linolenic FA (C 18: 3, ω 3) decreased by 1.3. Essential FAs are capable of being metabolized by means of the processes of desaturation and elongation to longer-chain and unsaturated derivatives. Eicosapentaenic acid (C 20: 5) and docosahexaenoic acid (C 22: 6, ω 3) are synthesized from linolenic acid. In these groups, eicosapentaenoic (C 20:5) was not determined, and the content of docosahexaenoic (C 22: 6, ω 3) decreased by 24.3 and 32.3 %, accordingly.

In relation to ω 3 USFA, the total content of ω 6 USFA increased mainly due to dihomo-γ-linolenic (C 20: 3, ω 6) content in 3.1 and 4.1 times, and arachidonic (C 20: 4, ω 6) - more than 1.6 and 1.9 times. The most important indicator that determines the degree of accumulation of ω 3 or ω 6 polyunsaturated FA in the brain was the concentration of docosahexaenoic FA (to the arachidonic FA) ratio. As the results are shown, this ratio was significantly changed from 1.01 in the control group to 0.5 and 0.34 in the 2nd and 4th groups, accordingly. These results testify the partial substitution of arachidonic and docosahexaenoic acids in brain phospholipids. This contributes to the increased formation of pro-inflammatory mediators, the so-called tissue hormones (eicosanoids), such as prostaglandins, prostacyclins, thromboxanes and leukotrienes, that affect platelet sticking and play an important role in the immune-inflammatory response of the body [19].

At the same time, there was a decrease in the total content of long-chain (C_{22}-C_{24}) FA in the brain lipids. Such changes occurred in all experimental groups, but they were most significant in the 2nd and, especially, in the 4th group, where it was more than 1.26 and 1.4 times lower than in the control group. These disorders may play an important role in the development of cognitive disorders and neurodegenerative diseases with the combined action of the components of the PM [20].

Discussion. In the molecular mechanisms of the pathogenesis of neurotoxic damages, caused by chemical factors, are playing an important role in modern industrial and ecologically dependent pathology. The metabolic disturbances of such lipid metabolites as FA, that are one of the main components of the cell membranes phospholipids, may have some negative consequences for the organism, exposed by the PM. The study of the specifics effect of the DBP and Cd combination, which have different types of biological action, showed that polyunsaturated FAs are the most sensitive links of the brain metabolism during the toxic-allergenic reactions development with signs of a systemic inflammatory process. These mechanisms are actively involved in the regulation of permeability and functional activity of cell membranes. The imbalance in the FA content and ratio correlation at the initial

stages of caused by PM toxicogenesis can be of a regulatory nature, which over time can become a predictor of deeper changes in the functioning of the central nervous system.

In this regard, behavioral and motor disorders, which are well detected long before neuron death, become important value. Changes in the animal's behavioral and psycho-emotional responses, identified in the dynamics of the experiment, are evidence of the development of neuro-immune dysregulation during the chronic exposure to components of PM, which acts predominantly as factors of low intensity.

Conclusions

1. A comparative analysis of the research results showed that, in the background of the development of a delayed-type of hypersensitivity, a typical for many components of PM immune-allergic reaction, sensitive markers of neuro-immune dysregulation were found in the experimental model, which are characterized by changes in the spectrum and ratio of fatty acids in brain tissues.

2. The identified spectrum imbalance and the ratio of unsaturated fatty acids correlate with deeper changes in the integrative activity of the central nervous system, which are manifested by the suppression of behavioral and psychomotor reactions in animals of the 2nd and 4th groups in the dynamics of the development of a delayed-type of hypersensitivity.

3. The conducted studies allow us to recommend the use of indicators of lipid metabolism disorders in the rat brain, in particular, the content and ratio of fatty acids, as informative biomarkers under the action of chemical factors of low intensity, including the needs of hygienic certification of PM.

4. When planning preventive measures, along with metabolic correction of interstitial metabolism, it is necessary to include preparations containing the complex ω 3 / ω 6 / ω 9 FA, which will allow for timely restoration of the adaptive-compensatory reserves of the body and reduce the likelihood of developing neuropathies during brain cell damage of toxic-allergenic origin.

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