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IMPACT OF SUCCINATE DERIVATIVES ON OXIDANT/ ANTIOXIDANT BALANCE SYSTEM IN THE RAT PANCREAS AND LIVER

Topicality. The succinate derivatives are widely used as a basis for the metabolite type drugs development which possess various pharmacological effects. The start of drugs production and their medical use depends directly on their safety for health. The xenobiotic safety assessment involves the identification of such changes that may be associated with mechanisms of adaptation or damage in organs and systems of the organism.

Aim. To determine the nature of succinate derivatives' impact on the indices of the lipid peroxidation and antioxidant system in pancreas and liver of rats.

Materials and methods. The succinate derivatives were administered to rats orally 30-fold. The biological material studied were the homogenate of pancreas and liver. We determined the content of the dienic conjugates, lipid hydroperoxides and thiobarbituric acid reactive substances. We also verified the activeness of catalase, superoxide dismutase, glutathione peroxidase and glutathione S-transferases.

Results and discussion. We found the influence of succinate derivatives in sub-toxic doses characterized by increased intensity of the lipid peroxidation in the pancreas interconnected with the changes in the activity of these reactions in the liver. These effects were determined due to the antioxidant enzymes activity decrease. The compounds' impact differed in the degree of disorders in the oxidative-antioxidant organs homeostasis. We have registered that the influence of relatively low doses of the succinate derivatives caused less severe and multidirectional changes in the lipid peroxidation indices and signs of the enhanced the antioxidant protection in the studied organs.

Conclusions. The succinate derivatives course changes in the activity of the free radical oxidation and antioxidant system in pancreas and liver thus can affect the state of the metabolic processes in organism.

Key words: succinate derivatives; pancreas; liver; lipid peroxidation; antioxidant enzymes

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Вплив сукцинат-похідних на систему оксидантно-антиоксидантного балансу в підшлунковій залозі та печінці щурів

Актуальність. Сукцинат-похідні широко застосовуються для розробки на їх основі лікарських засобів метаболічного типу дії з різноманітними фармакологічними ефектами. Впровадження лікарських засобів у виробництво та медичну практику напряму залежить від їх безпечності для здоров'я. Оцінка безпечності ксенобіотиків передбачає виявлення таких змін, які можуть впливати на механізми адаптації або пошкодження органів та систем організму.

Мета роботи – з'ясувати характер впливу сукцинат-похідних на показники ліпопероксидації та антиоксидантної системи у підшлунковій залозі та печінці щурів.

Матеріали та методи. Сукцинат-похідні вводили щурам перорально 30-разово. Біоматеріалом служили гомогенат підшлункової залози та печінки. Визначали вміст дієних кон'югатів, гідропероксидів ліпідів, активних сполук, які реагують з тіобарбітуровою кислотою, активність супероксиддисмутази, каталази, глутатіонпероксидази та глутатіон-S-трансферази.

Результати та їх обговорення. Встановлено, що вплив сукцинат-похідних в субтоксичних дозах характеризується підвищенням інтенсивності ліпопероксидації у підшлунковій залозі, що взаємопов'язано зі змінами активності цих реакцій у печінці щурів. Такі ефекти обумовлені зниженням активності антиоксидантних ферментів. Дія сполук відрізняється за ступенем порушення окисно-антиоксидантного гомеостазу органів. У відносно малих дозах сполук зареєстровані менш виражені, різноспрямовані зміни показників ліпопероксидації та ознаки покращення антиоксидантного захисту органів.

Висновки. Сукцинат-похідні викликають зміни стану вільно-радикального окиснення та антиоксидантної системи у підшлунковій залозі та печінці, що може впливати на перебіг метаболічних процесів в організмі.

Ключові слова: сукцинат-похідні; підшлункова залоза; печінка; перекисне окиснення ліпідів; антиоксидантні ферменти

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Влияние сукцинат-производных на систему оксидантно-антиоксидантного баланса в поджелудочной железе и печени крыс

Актуальность. Сукцинат-производные широко применяются для разработки на их основе лекарственных средств метаболического типа действия с разнообразными фармакологическими эффектами. Внедрение лекарственных средств в производство и медицинскую практику напрямую зависит от их безопасности для здоровья. Оценка безопасности ксенобіотиков предусматривает выявление таких изменений, которые могут влиять на механизмы адаптации или повреждения органов и систем организма.

Цель работы – выяснить характер влияния сукцинат-производных на показатели липопероксидации и антиоксидантной системы в поджелудочной железе и печени крыс.

Материалы и методы. Сукцинат-производные вводили крысам перорально 30-кратно. Биоматериалом служили гомогенат поджелудочной железы и печени. Определяли содержание диеновых конъюгатов, гидроперекисей липидов, активных соединений, реагирующих с тиобарбитуровой кислотой, активность каталазы, супероксиддисмутазы, глутатионпероксидазы и глутатион-S-трансферазы.

Результаты и их обсуждение. Установлено, что влияние сукцинат-производных в субтоксических дозах характеризуется повышением интенсивности перекисного окисления липидов в поджелудочной железе, которое взаимосвязано с изменениями активности этих реакций в печени крыс. Такие эффекты обусловлены снижением активности антиоксидантных энзимов. Действие соединений отличается по степени нарушений окислительно-антиоксидантного гомеостаза органов. В относительно малых дозах соединений зарегистрированы менее выраженные, разнонаправленные изменения показателей перекисного окисления липидов и признаки улучшения антиоксидантной защиты органов.

Выводы. Сукцинат-производные вызывают изменения интенсивности свободнорадикального окисления и активности антиоксидантной системы в поджелудочной железе и печени, тем самым могут влиять на состояние метаболических процессов в организме.

Ключевые слова: сукцинат-производные; поджелудочная железа; печень; перекисное окисление липидов; антиоксидантные энзимы

INTRODUCTION

An important strategic direction of modern pharmacology lies in the development of drugs based on synthetic analogues of nature metabolites and their derivatives capable (without any side effects) to reduce disorders in certain links of metabolism via stimulation of the adaptation mechanisms. The succinate derivatives (SD's) possess different kinds of such biological activity as antioxidant, detoxifying, membrane-stabilizing, energy- and immune-stimulating ones, which play a significant part in mechanism of their regulatory impact on liver functional state, pancreas, adrenal glands, cardiovascular system, hemostasis e.a. Today the succinic acid and its metabolites are often made the basis of the renowned drugs with the anti-hypoxic, anti-diabetic, anti-inflammatory, cardio- and hepatoprotective actions [1-4].

The expressed anti-diabetic properties were identified in β -phenylethylamide of 2-oxy succinanyl acid (β -PhEA-OSAA) synthesized by the State Institution "V. Danilevsky Institute of Endocrine Pathology Problems of National Academy of Medical Sciences of Ukraine". The mechanism of its metabolic action is associated with stimulation of energetic metabolism, oxidative stress suppression in mitochondria as well as with reduction of the non-enzymatic glycosylation [5]. The following are The first phase of β -PhEA-OSAA biotransformation brings out its two metabolites, 2-hydroxyphenylsuccinamid (2-HPhSA) and β -phenylethylsuccinamid (β -PhESA), that also belong to SD's and may affect specific effects and toxic potential of their parent compound.

β -PhEA-OSAA plays an active component of the anti-diabetic medicine with effectiveness established by various diabetes models and confirmed by the clinical tests. One of the main requirements for new promising drugs covers their safety for health therefore presupposing the toxicological expertise of their ability to damage separate organs and organism systems.

One of the initial pathobiochemical mechanisms of all xenobiotics impacts is believed to lie in the pro-/antioxidant homeostasis disorders that lead to changes in

various links of metabolism [6]. The biochemical processes are most active in the liver which is involved in detoxification of xenobiotics including most medicines. However, the drug biotransformation forms their toxic metabolites capable to disrupt some functions of the liver so forth affecting the functional state of many organs and systems. The normal as well as pathological liver has a close functional connection with the pancreas, and changes of these central organs of the digestive system state can essentially affect the activity of metabolism in the organism. Damages in liver and pancreas, regardless their genesis, may be initiated by an oxidative stress due to generation of an active form of oxygen and nitrogen with a decrease in level of the pro-inflammatory cytokines. On the other hand, it is known that the pancreas is more susceptible to intoxication than the liver as it differs by a low activity of the antioxidant enzymes and glutathione-synthetic processes that contribute to an intensive advancement of the oxidative stress in this organ [7]. The interconnection between changes of prooxidant-antioxidant system in the liver and in the pancreas under influence of the succinic acid derivatives has not been exposed. The study of this issue is useful for delineation of mechanisms of the biological action and safety of all compounds like these, and especially it is important for the promising antidiabetic medicines developed on their base.

The aim is to investigate the succinate derivatives' effects on the activity of the antioxidant enzymes and intensity of the lipid peroxidation reactions in the pancreas and liver tissue in the sub-acute experiment conditions.

MATERIALS AND METHODS

The sub-acute experiment was conducted over 48 outbred white male rats with body weight 190-210 g. The study complied with the "General Ethical Principles of Animal Experiments" (Ukraine, 2001). β -PhEA-OSAA was orally administered to rats 30-fold in doses 100 mg/kg and 25 mg/kg (1/100 and 1/400 DL₅₀ resp.). HPhSA was applied in doses 68 mg/kg and 17 mg/kg, and β -PhESA

was dosaged 72 mg/kg and 18 mgr/kg. These doses are equimolar to the above mentioned amounts of their original compound. The control and each test groups consisted of 8 animals. After finishing of the experiment the rats were decapitated under the light ether anesthesia, and their liver and pancreas homogenate was obtained for the study of biochemical parameters.

The state of the lipid peroxidation (LPO) processes was assessed by the content of the dienic conjugates (DC) [8], lipid hydroperoxides (LHP) [9] and thiobarbituric acid reactive substances (TBARS) in 10% homogenate of the liver and pancreas [10]. We also examined the activity of such antioxidant enzymes as catalase (EC 1.11.1.6) [11] and superoxide dismutase (SOD) (EC 1.15.1.1) [12] in the liver and pancreas, glutathione peroxidase (GPx) (EC 1.11.1.9) [13] and glutathione S-transferase (GST) (EC 2.5.1.18) in the liver [12]. Apart from that, we defined the protein content in liver homogenate [14].

Statistical analysis of the obtained results was conducted with the Anova system. Normal distribution of a trait in the sequences was determined using the Shapiro-Wilk (W) criterion. Pair comparison of experimental groups with the control was performed using the Student's t-criterion. The results are presented as the arithmetic mean and its probable statistical error ($\bar{X} \pm S\bar{x}$). We considered reliable all data at $p \leq 0.05$, and close to the statistically significant all data at $0.05 < p \leq 0.1$.

RESULTS AND DISCUSSION

We found that under SD's sub-acute impact the intensity of oxidative processes changed in the pancreas and the liver tissues of rats in parallel. The application of β -PhEA-OSAA at a dose 100 mg/kg as well as action of its two metabolites in equimolar amounts proved to intensify the LPO in the pancreas tissue. β -PhESA (72 mg/kg) and 2-HPhSA (68 mg/kg) caused an increase in content of TBARS by 31 % and 44 % ($P \leq 0.05$) and to a lesser extent, of LHP by 17 % and 10 % ($0.05 < P \leq 0.1$) in the organ homogenate. Our study of state of the antioxidant system (AOS) in the pancreas tissue registered a decrease in the activity of catalase under 2-HPhSA impact ($P \leq 0.05$) and of SOD under β -PhESA influence ($0.05 < P \leq 0.1$). The metabolites of β -PhEA-OSAA to a certain extent impacted the manifestation of this compound's pro-oxidant effect characterized by a significant increase of TBARS content by 22 % and a reduction of SOD activity in the pancreas homogenate (Tab. 1).

Under the same conditions of β -PhESA and 2HPhSA exposure, in the liver the changes of the pro-oxidant status were manifested as a tendency to increase in the content of TBARS ($0.05 < P \leq 0.1$) and were less expressed than in the pancreas. β -PhESA in the liver tissue also caused a significant increase in the activity of catalase, but GPx that is close by functional purpose to this enzyme changed its activity in the opposite direction under the im-

Table 1

PARAMETERS OF LIPOPEROXIDATION PROCESSES AND ANTIOXIDANT SYSTEM STATE IN RAT PANCREAS AND LIVER UNDER SUB-ACUTE IMPACT OF β -PHENYLETHYLAMIDE OF 2-OXYSUCCINANYL ACID (β -PHEA-OSAA) AT A DOSE 1/100 DL₅₀, 2-HYDROXYPHENYLSUCCINAMID (2-HPHSA) AND β -PHENYLETHYLSUCCINAMID (β -PHESA) AT EQUIMOLAR DOSES ($\bar{X} \pm S\bar{x}$, n = 8)

Parameters	Control 1	β -PhEA-OSAA, 100 mg/kg	Control 2	2-HPhSA, 68 mg/kg	Control 3	β -PhESA, 72 mg/kg
Pancreas homogenate						
Dienic conjugates, $\mu\text{mol/g}$ tissue	44.6 \pm 5.8	38.8 \pm 3.9	54.7 \pm 2.4	50.1 \pm 1.8	56.3 \pm 4.2	48.6 \pm 5.5
TBA-reactive substances, $\mu\text{mol/g}$ tissue	68.7 \pm 3.7	83.6 \pm 5.4*	73.8 \pm 6.7	106.3 \pm 4.9*	65.4 \pm 3.5	86.0 \pm 7.2*
Lipid hydroperoxides, $\mu\text{mol/g}$ tissue	54.7 \pm 4.0	55.9 \pm 3.9	40.1 \pm 1.1	43.9 \pm 1.5**	54.9 \pm 1.1	64.1 \pm 3.9**
Catalase, $\mu\text{mol/min}\cdot\text{g}$ tissue	55.9 \pm 0.9	57.0 \pm 1.8	55.8 \pm 0.2	50.1 \pm 0.2*	58.5 \pm 0.2	58.6 \pm 0.2
Superoxide dismutase, arbit. units/min \cdot mg tissue	156.4 \pm 6.9	82.9 \pm 6.2*	139.6 \pm 4.6	129.8 \pm 7.7	133.7 \pm 4.6	119.1 \pm 6.2**
Liver homogenate						
Dienic conjugates, nmol/mg protein	0.22 \pm 0.01	0.17 \pm 0.01*	0.18 \pm 0.02	0.19 \pm 0.03	0.14 \pm 0.02	0.13 \pm 0.01
TBA-reactive substances, nmol/mg protein	0.31 \pm 0.03	0.20 \pm 0.02*	0.26 \pm 0.03	0.39 \pm 0.07**	0.43 \pm 0.03	0.52 \pm 0.03**
Lipid hydroperoxides, nmol/mg protein	0.53 \pm 0.05	0.53 \pm 0.04	0.38 \pm 0.06	0.55 \pm 0.1	0.53 \pm 0.05	0.48 \pm 0.05
Catalase, nkat/mg protein	4.68 \pm 0.30	3.58 \pm 0.09*	3.79 \pm 0.63	3.03 \pm 0.35	3.41 \pm 0.20	4.15 \pm 0.22*
Superoxide dismutase, arbit. units/min \cdot mg protein	284 \pm 25	275 \pm 18	378 \pm 82	461 \pm 74	428 \pm 50	362 \pm 36
Glutathione peroxidase, nmol/min \cdot mg protein	143.9 \pm 6.4	113.9 \pm 1.7*	164.1 \pm 27.9	153.6 \pm 21.9	102.0 \pm 8.8	79.0 \pm 7.7**
Glutathione-S-transferase, nmol/min \cdot mg protein	45.6 \pm 3.8	36.7 \pm 0.66*	57.8 \pm 7.6	71.9 \pm 8.0	78.5 \pm 8.4	88.8 \pm 10.4

Notes: (here and at Tab. 2): * - $P \leq 0.05$; ** $0.05 < P \leq 0.1$ compared to the control.

part of that compound. β -PhEA-OSAA, on the contrary, slowed down the rate of the primary and intermediate reactions of the LPO, as evidenced by a significant (23 %) reduction in the content of DC and by more than one third of TBARS content in the organ homogenate. These changes may be connected to the expenditure of resources of the antioxidant system (AOS): a reducing activity of the anti-peroxide enzymes (catalase and GPx) and also of GST responsible for the second phase of metabolites detoxification including LPO products (Tab. 1). The deceleration of the free radical oxidation in its turn is reflected in the state of the liver antioxidant protection [15].

With a four-fold decrease of the administrated doses of SD's the increasing rate of generation of LPO products in the pancreas and the liver tissues was only registered under the influence of 2-HPhSA at a dose 17 mg/kg (Tab. 2). The content of TBARS in the pancreas homogenate increased by 23 % ($p < 0.05$), but this effect was twice less pronounced compared to the same direction changes after the application of that compound in a higher dose. These changes were accompanied by one and half-fold augmentation of the SOD activity in the pancreas homogenate ($p < 0.05$), which is a sign of the increased resistance of the organ against reactive oxygen and nitrogen species. Under the impact of 2-HPhSA at a small dose in the liver

tissue we registered a rising tendency in the content of TBARS and LHP ($0.05 < P \leq 0.1$), but also a substantial boosting in the anti-peroxide defense of the organ due to a compensatory stimulation of GPx and catalase activity by 1.6 and ($p < 0.05$) 1.4 times ($p < 0.05$) respectively.

Under the influence of β -PhESA at a dose 18 mg/kg, on the contrary, we recorded a reduction of LHP content in the liver homogenate ($0.05 < p < 0.1$). The application of β -PhEA-OSAA (25 mg/kg) also proved to slow down the LPO reactions, as evidenced by a 26 % reduction of the DC content in the liver homogenate ($0.05 < p < 0.1$) and by a 15 % diminution of LHP content in the pancreas homogenate ($0.05 < p < 0.1$). In the rat liver after the introduction of β -PhEA-OSAA we noted a significant decrease in SOD activity which perhaps serves as an adaptive reaction linked to a lessening need in dismutation of an excessive amount of superoxide anion radicals. However, the GST activity in the liver homogenate increased, and this change shows the activation of the II phase of detoxification (Tab. 2).

Toxicological study of SD's effects by criteria of the oxidative and anti-oxidative homeostasis shiftings enabled us to delineate pancreas as their primary target organ. In sub-toxic doses these compounds proved to stimulate the LPO processes through decreasing the resistance of an organ with cells deprived of an effective ferment pro-

Table 2

PARAMETERS OF LIPOPEROXIDATION PROCESSES AND ANTIOXIDANT SYSTEM STATE IN RAT PANCREAS AND LIVER UNDER SUB-ACUTE IMPACT OF β -PHENYLETHYLAMIDE OF 2-OXYSUCCINANYL ACID (β -PHEA-OSAA) AT A DOSE 1/400 DL₅₀, 2-HYDROXYPHENYLSUCCINAMID (2-HPHSA) AND β -PHENYLETHYLSUCCINAMID (β -PHESA) AT EQUIMOLAR DOSES ($\bar{X} \pm S\bar{X}$, n = 8)

Parameters	Control 1	β -PhEA-OSAA, 25 mg/kg	Control 2	2-HPhSA, 17 mg/kg	Control 3	β -PhESA, 18 mg/kg
Pancreas homogenate						
Dienic conjugates, $\mu\text{mol/g}$ tissue	44.6 \pm 5.8	37.0 \pm 5.3	44.9 \pm 4.7	42.3 \pm 2.4	39.4 \pm 2.6	42.1 \pm 2.9
TBA-reactive substances, $\mu\text{mol/g}$ tissue	68.7 \pm 3.7	71.0 \pm 4.3	64.1 \pm 2.6	78.2 \pm 3.2*	62.5 \pm 2.8	61.1 \pm 3.2
Lipid hydroperoxides, $\mu\text{mol/g}$ tissue	54.7 \pm 4.0	46.3 \pm 2.6**	48.4 \pm 1.4	46.0 \pm 2.9	67.3 \pm 1.4	68.9 \pm 6.3
Catalase, $\mu\text{mol/min}\cdot\text{g}$ tissue	55.9 \pm 0.9	56.0 \pm 0.8	62.8 \pm 2.8	68.3 \pm 4.4	44.6 \pm 1.8	44.4 \pm 1.1
Superoxide dismutase, arbit. units/min \cdot mg tissue	156.4 \pm 6.9	138.9 \pm 12.2	70.9 \pm 7.2	99.9 \pm 7.1*	124.3 \pm 5.6	121.3 \pm 4.9
Liver homogenate						
Dienic conjugates, nmol/mg protein	0.19 \pm 0.01	0.14 \pm 0.02**	0.16 \pm 0.02	0.16 \pm 0.01	0.13 \pm 0.02	0.10 \pm 0.02
TBA-reactive substances, nmol/mg protein	0.26 \pm 0.01	0.25 \pm 0.02	0.22 \pm 0.03	0.29 \pm 0.02**	0.26 \pm 0.02	0.26 \pm 0.05
Lipid hydroperoxides, nmol/mg protein	0.63 \pm 0.09	0.58 \pm 0.14	0.51 \pm 0.06	0.70 \pm 0.09**	0.50 \pm 0.06	0.35 \pm 0.04**
Catalase, nkat/mg protein	4.64 \pm 0.37	4.34 \pm 0.35	3.68 \pm 0.17	4.97 \pm 0.26*	4.06 \pm 0.21	4.09 \pm 0.37
Superoxide dismutase, arbit. units/min \cdot mg protein	429 \pm 20	325 \pm 39*	420 \pm 33	465 \pm 78	387 \pm 17	369 \pm 51
Glutathione peroxidase, nmol/min \cdot mg protein	111.1 \pm 9.8	110.5 \pm 14.4	125.2 \pm 13.4	202.8 \pm 30.3*	125.2 \pm 13.4	101.8 \pm 6.8
Glutathione-S-transferase, nmol/min \cdot mg protein	45.7 \pm 4.8	64.9 \pm 8.2**	75.9 \pm 10.6	68.7 \pm 5.4	75.9 \pm 10.6	55.7 \pm 11.5

tection from the free radicals. However, we registered the much lesser respective activity of β -PhEA-OSAA than of its metabolites, β -PhESA and 2-HPhSA. Hence we hypothesized that the β -PhEA-OSAA mono-introduction when it is accompanied with its metabolites formation in an organism would bring their smaller summarizing effect on the LPO reactions than in case of their isolated introduction, i.e. there exists the antagonism of impact as an element of their combined action [16]. It should also be noted that the β -PhEA-OSAA metabolism is fractional, and out of its two metabolites the highest concentration and durability of presence in the system blood flow is attributed to β -PhESA which obviously plays the larger part in the pro-oxidant effect of the maternal compound [17]. When administered in relatively small doses, β -PhEA-OSAA and β -PhESA did not essentially change the activity of the LPO reactions in the pancreas tissue, unlike 2-HPhSA that slightly intensified them so forth strengthening the anti-oxidant protection of the organ. And also, unlike β -PhESA, 2-HPhSA is promptly eliminated from an organism so cannot essentially affect the activity of the maternal compound re. the LPO-AOP system [17].

The changes of a metabolic activity of the liver are interrelated to the ones in the functional state of the pancreas. However, the liver as the main organ of the detoxification of xenobiotics, in contrast to the pancreas, has a high reserve-adaptive potential to prevent the generation of the products of free radical oxidation and thus to restrain the development of an oxidative stress in the conditions of intoxication [18]. After sub-acute introduction of the sub-toxic dose of β -PhEA-OSAA the LPO processes in the liver tissue, on contrary, slows down, and this effect due to certain expenses of antioxidant reserves in the organ and has dose-dependent character. With an introduction of β -PhESA in the organism at a relatively small dose its influence on the state of the LPO processes manifests in the same direction as for β -PhEA-OSAA. However β -PhESA at the sub-toxic dose as well as 2-HPhSA at both tested doses causes increasing in the content of the intermediate LPO products in the liver, but in parallel adaptation mechanisms are activated, which contributes to the increase the resistance of the organ against toxic free radicals impact.

Caused by the SD's influence, the changes of pro/antioxidant status in the pancreas and liver that are allied functionally as the central organs of the digestive system and metabolism, can provoke significant changes in most metabolic processes of the organism.

CONCLUSIONS

1. Within the sub-acute introduction, β -phenylethylamide of 2-oxy succinanyl acid (β -PhEA-OSAA) at a dose 100 mg/kg (1/100 DL₅₀) and its metabolites – 2-hydroxyphenylsuccinamid (2-HPhSA) and β -phenylethylsuccinamid (β -PhESA) at equimolar doses (72 mg/kg and 68 mg/kg resp.) stimulate lipid peroxidation reactions in the pancreas and also contribute to the reduction in activity of the antioxidant system in the organ, yet β -PhEA-OSAA gives a way by these criteria to its metabolites. With the four-fold reducing doses, the same (but less intensive) direction of changes in the lipid peroxidation processes are caused by 2-HphSA, that also proved to strengthen the antioxidant protection of the pancreas.
2. Under the sub-acute administration of β -PhEA-OSAA the lipid peroxidation processes in the liver are slowed down. This effect has a pronounced dose-dependent nature and is related to certain expenses of antioxidant resources in the organ, but these reserves far exceed the potential of the free radicals counteraction in other organs. β -PhESA at a dose 18 mg/kg influences the state of the lipid peroxidation processes in a similar way. After application of β -PhESA at a dose 72 mg/kg and 2-HphSA at a dose 68 mg/kg, in the liver the content of the intermediate products of the lipid peroxidation increases slightly, but antioxidant defense of the organ also augments due to activation of its adaptation mechanisms.
3. The most active of the studied compounds by the pro-oxidant action criteria (increase in content of the lipid peroxidation products in the pancreas and liver tissues) is 2-HPhSA, one of β -PhEA-OSAA metabolites, but time of its stay in the blood flow is significantly smaller than of two other studied compounds. Considering a nature of changes of the lipid peroxidation parameters and antioxidant enzymes activities, β -PhESA as a product of β -PhEA-OSAA biotransformation can essentially contribute to the effects of its parent compound over the pro/antioxidant status of the rat pancreas and liver.
4. The changes of the pro/antioxidant homeostasis induced by the succinate derivatives in the pancreas and liver that serve as the central organs of metabolism are interdependent and can affect the state of the majority of metabolic processes in the organism.

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