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Original Article

Changes in the Contractile Activity and Reactivity to 5-HT of Smooth Muscles of Rats Following Total Body Irradiation with Accelerated Electrons

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Background: Besides its “classical” neurotransmitter function in the central and peripheral nervous systems, serotonin, or 5-hydroxytryptamine (5-HT) is also a local hormone in a number of tissues, including those of the GI tract. Radiation is known to be able to disrupt certain functions of the tract, modulated by 5-HT-signaling pathways, or the serotonin receptors themselves.

Aim: The present investigation focused on clarifying the nature and extent of influence of an accelerated electron beam with energy of 9 MeV on the serotonergic mediation of healthy smooth muscle gastric tissue of rats following total body irradiation of the animals.

Materials and methods: The study involved a control group and two experimental groups of animals exposed to 1 and 5 Gy, respectively, using Siemens Primus S/N 3561. Circular smooth muscle tissues were isolated from rats 1 hour and 18 hours after they were exposed to 1 and 5 Gy and also 5 days after irradiation from the rats that received a dose of 5 Gy in order to investigate the action of exogenous serotonin at increasing concentrations from 10^{-8} to 10^{-4} mol/l. The contractile reactivity of each group SM preparations was registered isometrically.

Results: Electron beams with energy of 9 MeV did not damage the contractile apparatus of gastric SM of rats and had a stimulating effect on contractility resulting from rapidly developing processes (1 hour) or later occurring once (5 days).

Conclusions: Difference was observed in the importance of the factors of received dose, lapse of time from irradiation to investigation of SM tissues, and exogenous 5-HT concentration for the changes in SM reactivity in serotonin-induced tonic and phasic responses.

Key words:

accelerated electron beam, gastric smooth muscles, contractile activity, 5-HT

INTRODUCTION

Administration of radiation therapy in tumor treatment inevitably includes irradiation and damage to normal tissues. At high treatment doses, the information concerning damage to healthy tissues is important for the planning the radiation therapy itself, and warning against the possible determined, as well as stochastic consequences for the patient's health.

In distant radiotherapy, the tissues of the digestive system are unduly subject to irradiation, since the GI tract occupies a relatively large area of the human body and segments of it become inevitably involved by the radiation field.[1] Radiation treatment is able to cause a variety of gastrointestinal side effects.[2] The radiation-induced damage to the GI tract, even when the latter is not a target structure, has a negative effect on the patient's general condition, the development of the recovery process and quality of life. In this respect, studies investigating the damaging effects of ionizing radiation are quite topical.

One of the major functions of the GI tract is the motor one. Smooth muscle (SM) contractions mix the ingested food, move it along the tract, facilitate the absorption of nutrients, and cleanse the tract from food debris, secretions and bacteria between meals. That is why the excitation-contraction coupling in gastric and intestinal SM that underlies the tract movement has been an object of multilateral and thorough investigations of experimental and clinical nature.

Side by side with other biologically active substances (such as acetylcholine), serotonin has marked influence on the contractile activity of the GI tract.[3,4] Apart from being a neurotransmitter in the central and peripheral nervous system, serotonin is also a local hormone in a number of tissues, including those of the GI tract. An indication of the importance of this monoamine for the GI tract functions is the fact that almost 80% of the total body amount of 5-HT is contained within the tract tissues, most frequently in the enterochromaffin cells and less frequently in the enteric nerves and mucosal mast cells.[5] The presence of various types of serotonin receptors along the entire length of the tract has been demonstrated in different animal species.[6,7]

There is evidence of a reliable influence of ionizing radiation on the contractile activity of gastric and intestinal SM, as well as on GI tract motility.[8] Radiation is known to be able to disrupt certain functions of the tract, modulated by 5-HT-signaling pathways, or the serotonin receptors themselves.[9] Changes in the 5-HT tissue content along the course of the tract have been registered following total body gamma ray irradiation.[10] It has been accepted that following radiation-induced release from similar depots, including enteric neurons, 5-HT can influence digestive functions (the motor one as well), acting as a neurotransmitter, neuromodulator or paracrine agent on the cells responsible for the excitation-contraction coupling.[10,11] However, the evidence is contradictory and considerably influenced by the dose received, the animal species, age, type of radiation (gamma rays, electrons, protons), duration of the lapse of time following irradiation and other factors. To be more specific, no systematic investigations have been carried out on the changes occurring in 5-HT regulation of the excitation-contraction coupling in the GI tract under the impact of accelerated electron beams.

The aim of this study was to clarify the influence of electron beams accelerated by means of Siemens Primus S/N 3561 on the functioning of the 5-HT mediator system influencing the contractile activity of healthy gastric SM tissue of rats after total body irradiation of the animals.

MATERIALS AND METHODS

Animals and anesthetic protocol

Male Wistar rats with body weight in the range of 220-280 g were provided by the Animal House of Medical University– Plovdiv, Bulgaria. The rats were housed in standard laboratory conditions (23-25°C, 50-55% humidity and 12/12h light/dark cycle) and fed with standard commercial food and given water ad libitum. The animals were fixed on electrical thermophore maintaining the temperature of 37°C during the experiment. At the beginning of the experiments they were anaesthetized by xylazine 2% –10 mg/kg + ketamine (Calypsol) 5% – 100 mg/kg, injected intraperitoneally.

Study design

The study on the influence of accelerated electron beams on serotonergic mediation in excitation-contraction coupling was carried out with SM isolated from the stomach of control rats and rats exposed to total body irradiation. The animals received two radiation doses – 1 Gy and 5 Gy. Thus, the study involved a control group and two experimental groups (depending on the doses received).

To investigate the action of exogenous serotonin, the latter was added to a tissue bath (20 ml) at increasing concentrations from 10^{-8} to 10^{-4} mol/l. SM tissues were isolated 1 hour and 18 hours following irradiation, and in the group receiving a dose of 5 Gy, 5 days following irradiation as well. As far as this index is concerned (lapse of time after irradiation) the SM preparations were divided into 5 groups.

The maximums of serotonin-induced contractions (concentration/effect curves) were registered and compared, as well as the changes in the parameters of spontaneous (phasic) contractions (amplitude and frequency) of SM obtained from the experimental groups and the control one.

Treatment procedure

During anatomotopographic planning, an optimal position of the rat was chosen to ensure repeatability and reproducibility in subsequent irradiation. The rat was anesthetized and immobilized in an anterior-posterior position on a 30×30×0.5-cm plexiglass slab phantom, suitable for its size.

During the planning, Siemens Somatom Spirit Power computer tomograph was used. The selected protocol was Abdomen Routine Radiotherapy, spiral scan with parameters: 130 kV and 120 mA. A series of 80 transverse sequential slices were made, with thickness width 0.3 cm. The mean rat volume was approximately 207 cm^3.

The contour of the rat was outlined in each transversal slice obtained from computer tomography. For this purpose, a computer planning system CMS XiO was used, and the subsequent three-dimensional dosimetric planning was carried out.

Total body irradiation with electron beam was applied to the experimental animals. The electron energy was 9MeV. A standard electron applicator was used with sizes 25×25 cm. The planning treatment doses were 1 Gy and 5 Gy, in single fraction. The dose was defined in the depth of the dose maximum (2 cm). The mathematical algorithm used to calculate the absorbed dose was Pencil Beam.

The procedures were performed with Siemens Mevatron Primus multimodal linear accelerator. Each treatment was carried out in the presence of specialists - medical physicist, physician and technicians.

Prior to irradiation, the rats were axially centered to provide identity position between planning and irradiation.

During the treatment, the subject was continuously monitored by the team through a visual link. After the end of the treatment, the rats were transported to a laboratory for further research.

Isometric registration of SM contractile activity

At the beginning of the *in vitro* experiments the animals were euthanized by overdose anesthesia (ketamine and xylazine). Smooth muscle preparations from circular muscle layer of a stomach-corpus were cut. They were 1.0-1.1 mm wide and 13-15 mm long.

All experiments were carried out according to the guidelines for using laboratory animals: directive 2010/63/EU.

Contractile activity of the preparations was registered isometrically by detectors Tenzo "Swema" - Sweden. Initial mechanical stress of the preparations reached by stretch tenzyosystem is corresponding to tensile force of 10 mN. Krebs solution (pH = 7.4) used for washing of SM preparations has been continuously aerated with a gas mixture of 95% O_2 and 5% CO_2 at 37°C. The 60-minute adaptation of tone level of preparations was taken as a starting tone and the changes as contraction or relaxation were compared to it. During the period of adaptation Krebs solution was changed several times. Drug-caused reactivity of SM preparations was counted and registered by gain stage "Microtechna" (Czech Republic) and recorded on paper recorder "Linseis" (Germany).

The following chemicals were used: serotonin (5-HT) (Sigma) and acetylcholine (Sigma). Krebs solution with the following composition (mM): NaCl 120; KCl 5.9; $CaCl_2$ 2.5; $MgCl_2$ 1.2; NaH_2PO_4 1.2; $NaHCO_3$ 15.4 and glucose 11.5 (Merck) was used.

Statistical analysis

The data were expressed as the mean ± standard error of the mean (SEM). The number of tissue preparations used in each experiment is indicated by **n**. Statistical differences were tested using Student's t-test, and a probability ($p < 0.05$) was considered significant. All statistical analyses were performed using a specialized software SPSS, version 17.0 (SPSS Inc. Chicago, IL).

RESULTS

SM dissected from the stomach of control (non-irradiated) rats responded with tonic contractions increasing in strength following consecutive treatments with increasing 5-HT concentrations (Fig. 1), with the exception of 10^{-4} mol/l, which tended to decrease the contractions, as compared to those caused by 10^{-5} mol/l. The data obtained are presented in Fig. 1 as concentration/effect curves.

An experimental recording of SM reactions following treatment with different 5-HT concentrations is presented in **Fig. 2**.

The SM tissues isolated from irradiated animals possessed a reactivity to 5-HT different from the reactivity of the control animals.

The strength of the 5-HT-induced tonic contractions of SM preparations isolated 1 hour after irradiation with doses 1 and 5 Gy significantly exceeded the strength in the respective non-irradiated (control) preparations, or showed a tendency to an increase (**Table 1**).

No significant differences were found between serotonin-induced contractions of SM tissues dissected from rats 18 hours after exposing to radiation in doses of 1 and 5 Gy and the respective contractions observed in the control animals (**Table 1**). The peculiarity found in the control tissues was preserved – the contraction evoked by 10^{-4} mol/l 5-HT did not differ significantly in strength from that evoked by 10^{-5} mol/l, with the exception of the response of the preparations isolated from rats 18 hours after irradiation dose of 5 Gy.

Increasing the length of time elapsing between the irradiation and the dissection of SM tissues to 5 days (exposure dose 5 Gy) resulted in significantly stronger contractions evoked by the 5-HT concentrations ranging between 10^{-8} and 10^{-4} mol/l, as compared to those induced by similar 5-HT contractions in non-irradiated preparations (**Table 2**). The reaction caused by 10^{-4} mol/l showed a tendency to an increase ($p = 0.06$) compared to that induced by 10^{-5} mol/l.

All control SM preparations (with the exception of only 1) possessed spontaneous phasic activity. Increasing the serotonin concentration from 10^{-8} to 10^{-5} mol/l increased the amplitude of phasic contractions from 0.67±0.48 mN to 1.92±1.07 mN ($p=0.03$; $n=15$). The application of 10^{-4} mol/l tended to reduce the amplitude to 1.03±0.90 mN, as compared to its value at the preceding concentration (**Table 3**).

In the range studied the monoamine did not influence the frequency of spontaneous phasic contractions (4-5 min^{-1})

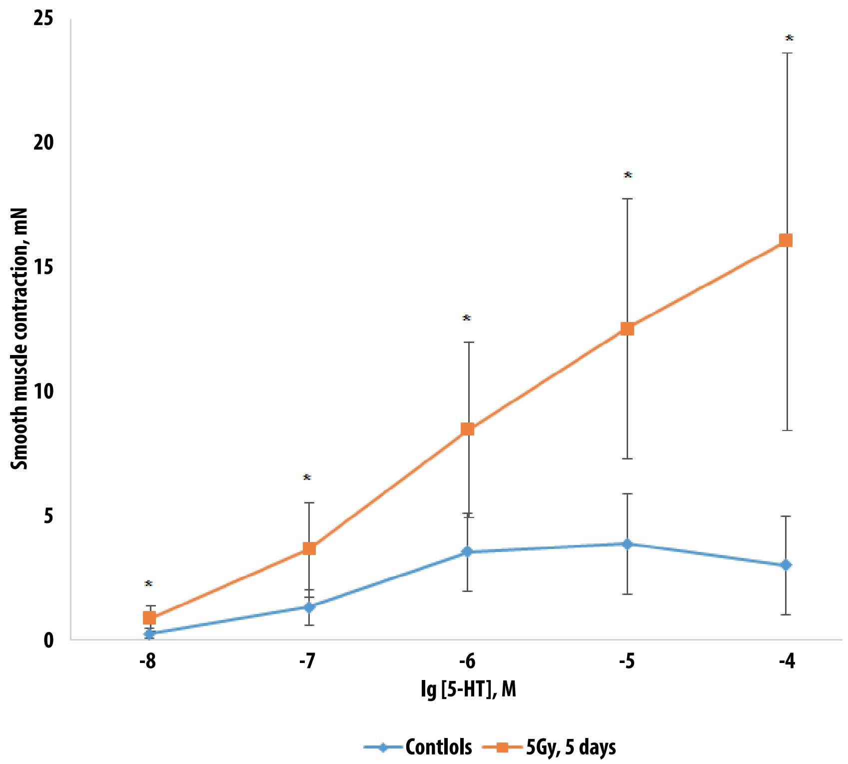

Figure 1. Concentration/effect curves following application of exogenous 5-HT to gastric preparations from control and irradiated rats (5 Gy) 5 days after irradiation. Each experimental data point shows the maximum contraction value obtained after application of the 5-HT concentration presented on the abscissa, for both groups of rats; $^*p < 0.05$.

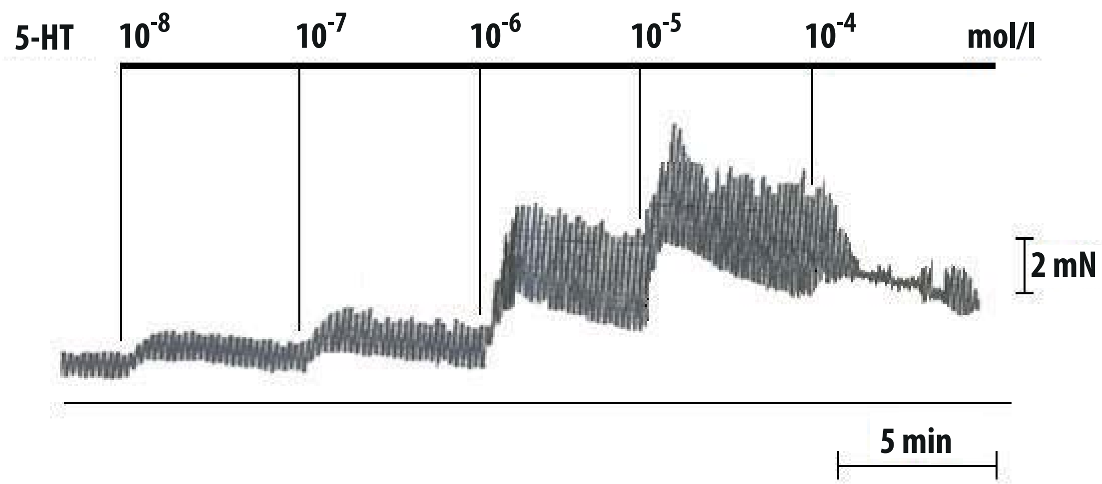

Figure 2. Influence of consecutively increasing 5-HT concentrations (10^{-8} – 10^{-4} mol/l) on the contractile activity of a control SM preparation.

of preparations obtained from the control group.

The irradiation with accelerated electrons involves in a different way the extent of 5-HT influence on the parameters of phasic activity.

After 1 hour and 18 hours, SM of rats exposed to the minimum dose of 1 Gy did not register a significant change in the amplitude of phasic activity, both at baseline and after application of all 5-HT concentrations used in the study (ranging between 10^{-8} and 10^{-4} mol/l), as compared to the amplitude of the control preparations.

The strength of phasic contractions in rats irradiated with 5 Gy, both at baseline and in serotonin presence, tended to increase proportionally to the time elapsed between irradiation and dissection of the SM preparations (5 days

Table 1. 5-HT-evoked SM tonic contractions of control preparations and preparations receiving various doses and dissected 1 and 18 hours following irradiation. The comparison involved the control SM preparations and their respective ones obtained from the different groups of irradiated rats for each 5-HT concentration separately. Significant differences are indicated by an asterisk * ($p < 0.05$)

Concetration, mol/l	Controls		n	1Gy; 1h		n	1Gy; 18h		n	5Gy; 1h		n	5Gy; 18 h		n
1.10^{-8}	0.28	±0.22	15	0.38	±0.29	12	0.3	±0.28	12	0.48	±0.21	6	0.13	±0.12	6
5.10^{-8}	0.96	±0.43	18	1.33	±0.75	12	1.17	±0.89	12	1.99	±0.92*	6	0.56	±0.29	6
1.10^{-7}	1.34	±0.71	15	2.03	±1.12	12	1.56	±1.18	12	2.93	±1.36*	6	0.96	±0.47	6
1.10^{-6}	3.55	±1.6	15	5.05	±2.18*	12	3.63	±2.48	12	6.57	±2.64	6	3.13	±1.3	6
1.10^{-5}	3.89	±2.01	16	6.08	±2.43*	12	4.17	±2.91	12	6.28	±2.11*	6	4.3	±2.3	6
1.10^{-4}	3.03	±2.0	15	5.71	±2.44*	12	3.62	±2.49	12	5.57	±2.4*	6	6.61	±3.44*	6

Table 2. 5-HT-evoked SM tonic contractions of control preparations and preparations receiving a dose of 5 Gy dissected 5 days after irradiation. The comparison involved the control and irradiated SM preparations for each 5-HT concentration separately. Significant differences are indicated by an asterisk * ($p < 0.05$)

Concentration, mol/l	Controls	n	5Gy; 5days	n
1×10^{-8}	0.28±0.22	15	0.91±0.47*	8
5×10^{-8}	0.96±0.43	18	2.53±1.31*	8
1×10^{-7}	1.34±0.71	15	3.68±1.90*	8
1×10^{-6}	3.55±1.6	15	8.48±3.52*	8
1×10^{-5}	3.89±2.01	16	12.56±5.24*	8
1×10^{-4}	3.03±2.0	15	16.08±5.60*	7

Table 3. Amplitude of phasic contractions at baseline and in the presence of serotonin of SM preparations from control and irradiated rats (exposure dose of 5Gy) 1 hour, 18 hours and 5 days after irradiation. The comparison involved the control and irradiated SM tissues for each 5-HT concentration separately. Significant differences are indicated by an asterisk * ($p < 0.05$)

Concentration, mol/l	Controls	n	5Gy; 1h	n	5Gy; 18h	n	5Gy; 5 days	n
norm	0.67±0.48	15	0.88±0.52	6	1.8±1.68*	6	1.7±1.18*	11
1.10^{-8}	0.7±0.51	15	0.92±0.38	6	1.8±1.55*	6	2.07±1.32*	11
5.10^{-8}	0.94±0.56	12	1.05±0.32	6	2.3±1.90*	6	2.69±1.63*	11
1.10^{-7}	0.99±0.7	15	1.4±0.81	6	2.3±1.78*	6	2.87±1.85*	10
1.10^{-6}	1.53±1.68	15	1.4±0.56	6	2.7±2.04	5	3.26±2.32*	11
1.10^{-5}	1.92±2.07	15	0.35±0.32	6	2.5±1.90	6	3.02±2.27	11
1.10^{-4}	1.03±0.9	15	0.07±0.19	6	0.9±1.13	6	1.05±1.85	10

>18 hours > 1 hour). Statistically significant changes were observed at lower 5-HT concentrations (10^{-8}- 10^{-6} mol/l). The higher concentrations resulted in decreased amplitude of phasic contractions, as compared to the maximum one for the respective group (**Table 3**), and in some preparations phasic activity lacked.

Treating SM tissues obtained from all groups of irradiated animals with 5-HT at concentrations in the range from 10^{-8} mol/l to 10^{-4} mol/l did not cause any changes in the frequency of their phasic contractions, which fluctuated between 4 and 5 contractions in a minute.

DISCUSSION

Electron beams with energy of 9 MeV influence the contractile processes in gastric SM, causing changes in the characteristics of phasic activity and the reactivity to serotonin that determines the nature of a number of GI tract functions, including regulation of the motor function.[12,13]

The results obtained give us ground to contend that this influence is determined by three factors: the dose received, the time elapsed between irradiation and SM tissue dissection and the exogenous 5-HT concentration.

Spontaneous contractile activity is inherent to gastric SM. A received dose of 1 Gy did not influence its frequency and the changes in strength (amplitude) were differing in direction and negligible in value. A higher dose (5 Gy) was needed and a longer period of time (at least 18 hours, as our experiments found) for a significant increase in amplitude. Enhancement of spontaneous phasic contractions in gastric SM is usually associated with an increase in transmembrane Ca^{2+} current entering the cells through L-type Ca^{2+} channels.[14] Thus, it can be argued that a dose of 5 Gy received from an electron beam influences the kinetics of these channels by increasing their conductivity without any negative influence on the SM contractile apparatus.

Our experimental data provide indirect information that accelerated electrons of the energies we used do not involve significantly the functions of the interstitial cells of Cajal responsible for the frequency of spontaneous contractions, which remains constant.[15] There seems to be a certain resistance of the structures conducting a slow wave in the gastric wall to the action of this irritant.[16]

The magnitude of serotonin-induced effects on the phasic contractile activity of SM obtained from the animals exposed to a dose of 5 Gy occurred as an increase in their strength, which was proportional to the received dose and the duration of the period between irradiation and isolation of the preparations. Statistically significant differences, however, were observed only in the action of the lower concentrations of exogenous serotonin (10^{-8} mol/l – 10^{-7} mol/l at 5 Gy/18 hours and 10^{-8} mol/l – 10^{-6} mol/l at 5 Gy/5 days). The nature of the general dependence was identical with the one observed in the SM tissues not treated with 5-HT (**Table 3**, norm), which makes an analogical explanation possible – an activating effect of radiation on processes providing entry of Ca^{2+} through membrane-potential dependent Ca^{2+} channels and an increase in the strength of phasic contractions.

The lack of significant differences in the serotonin-induced effects observed at higher 5-HT concentrations in SM obtained from control and irradiated animals cannot be a result of a damaging effect of radiation on the contractile apparatus, since this is in contradiction to the results of other experiments we have carried out. This lack can be associated with the action of 5-HT – in non-irradiated tissues it also tended to reduce the strength of spontaneous contractions in the maximum concentration used (10^{-4} mol/l). However, in irradiated tissues this effect occurred at concentrations 10 to 100 times lower than that applied to non-irradiated tissues - evidence of radiation-induced decrease in the threshold of 5-HT-evoked processes reducing the strength of SM phasic activity.

The comparison between SM tonic contractions induced by equimolar 5-HT concentrations in irradiated and non-irradiated rats showed differences, obviously resulting from the interaction between the accelerated electron beam and the tissues.

The concentration/effect curve of serotonin-induced tonic contractions was of sigmoid nature in the control preparations (obtained from non-irradiated rats) – the maximum concentration of 10^{-4} mol/l evoked a contraction statistically indistinguishable from the submaximal one (10^{-5} mol/l). Characteristics of the serotonergic mediator system that can be used to explain this fact acceptably include: saturation of the ligand-receptor interaction of the 5-HT receptors present in SM, specific activation of 5-HT_7 receptors by higher serotonin concentrations, internalization of contraction-inducing receptors or their desensitization, as well as activation of the electrogenic Na/K pump with subsequent hyperpolarization.[17-21]

The strength of tonic contractions caused by exogenous serotonin increased following irradiation. A leading factor for this alteration is the duration of the period after irradiation. A significant increase was found in SM isolated 1 hour after irradiation, irrespective of the value of the dose received (1 or 5 Gy), whereas the contractions of the tissues isolated 18 hours after irradiation did not differ statistically from the respective controls. This is a proof of the importance of the lapse of time after irradiation as a factor for occurrence of changes in the reactivity to serotonin. Our results showed that the dependence of the strength of 5-HT-evoked tonic contractions on time is not a linear one. The time dependence registered was obviously a product of a rapid process caused by the accelerated electrons and leading to a temporary sensitization of the serotonergic signaling cell system, which subsided hours later (in less than 18 hours).

An exception to this rule was observed only in the contraction induced by 10^{-4} mol/l serotonin applied to SM receiving a dose of 5 Gy. The contraction significantly the respective control reaction, as well as the one caused by 10^{-5} mol/l. The latter is likely to result from the combined action of the higher exposure dose (5 Gy) and the maximal serotonin concentration, which, as it has already been said, triggers processes of threshold nature.

Increasing the period between the irradiation and the dissection of SM to 5 days registered yet another increase in their reactivity to serotonin. In this case, the 5-HT-induced tonic contractions significantly exceeded in magnitude the respective controls. The concentration/effect dependence observed in these tissues was no more sigmoid in nature but transformed into a straight line. The manifold increase in the reactivity of the irradiated tissues most likely results from an increased expression evoked by radiation or sensitization of the serotonin receptors present in the SM cells, or else, it might be a result of both processes simultaneously.[22]

CONCLUSIONS

5-HT potentiates the contractile activity of gastric SM of rats. Electron beams with an energy of 9 MeV do not damage the contractile apparatus of gastric SM of rats and influence contractility in a stimulating way as a result of processes of rapid development (1 hour) or later occurrence (5 days). Difference was observed in the importance of the factors of received dose, lapse of time from irradiation to investigation of SM tissues, and exogenous 5-HT concentration for the changes in SM reactivity in serotonin-induced tonic and phasic responses.

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Изменения сократительной активности и реактивности 5-HT гладких мышц крыс после тотального облучения тела ускоренными электронами

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Введение: В дополнение к своей «классической» нейротрансмиттерной функции в центральной и периферической нервной системе, серотонин или 5-гидрокситриптамин (5-HT) также является локальным гормоном во многих тканях, в том числе в желудочно-кишечном тракте. Известно, что излучение нарушает определённые функции тракта, модулированные 5-HT сигнальными путями, или самими серотониновыми рецепторами.

Цель: Настоящее исследование посвящено объяснению природы и степени влияния луча ускоренных электронов с энергией 9 МэВ на серотогенное опосредование здоровой гладкомышечной желудочной ткани у крыс после тотального облучения тела животного.

Материалы и методы: В исследование были включены контрольная группа и две экспериментальные группы животных, подвергшихся воздействию 1 и 5 Gy, соответственно, на приборе Siemens Primus S / N 3561. Образцы круглой гладкой мышечной ткани были выделены у крыс через 1 и 18 часов после воздействия 1 и 5 Gy, а также через 5 дней после облучения от крыс, которых облучали в дозе 5 Gy, для изучения действия экзогенного серотонина при повышении концентрации от 10-8 до 10-4 mol/l. Сократительная активность препаратов гладких мышц каждой группы отражалась изометрически.

Результаты: Электронные лучи с энергией 9 MeV не повреждают сократительный аппарат гладких мышц желудка крысы и оказывают стимулирующее влияние на сократительную способность, что является результатом быстро развивающихся процессов (1 час) или более поздних, появляющихся однократно (5 дней).

Выводы: Была установлена разница в значениях факторов полученной дозы, периода времени от облучения до исследования тканей гладких мышц и экзогенной концентрации 5-HT в отношении изменений в реактивности гладких мышц при серотонин-индуцированных тонических и фазовых реакциях.