ДЛИТЕЛЬНАЯ АКТИВАЦИЯ ТУЧНЫХ КЛЕТОК КАК ЭКСПЕРИМЕНТАЛЬНАЯ МОДЕЛЬ ДЛЯ ИССЛЕДОВАНИЯ ИХ РОЛИ В РЕГУЛЯЦИИ СПЕРМАТОГЕНЕЗА

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Резюме. Тучные клетки являются важным компонентом иммунного микроокружения органов мужской репродуктивной системы и участвуют в их регуляции в норме и при патологии. Моделирование дисрегуляции в виде активации или ингибирования тучных клеток и исследование влияния данного нарушения на сперматогенез может помочь в установлении точных механизмов регуляции данного процесса. Одним из активаторов тучных клеток является препарат Ципрофлоксацин, который зарекомендовал себя в исследованиях тучных клеток сердца, однако ранее не использовался в работах по изучению сперматогенеза. Цель данного исследования – оценить влияния разных схем приема препарата Ципрофлоксацин на тучные клетки репродуктивных органов самцов крыс и выбрать оптимальную дозу и продолжительность приема для создания модели, которая позволит исследовать участие тучных клеток в регуляции сперматогенеза. Эксперимент проведен на самцах линии Wistar. Использовали разные концентрации ципрофлоксацина (200 и 400 мг/кг) и сроки его приема. На гистологических препаратах оценивали морфофункциональные параметры тучных клеток семенников и придатков семенников. Препарат Ципрофлоксацин модулирует активность тучных клеток в зависимости от времени, дозы и ткани. После приема препарата в дозе 200 мг/кг 7 суток увеличивается количество, синтетическая активность тучных клеток и процент клеток со зрелыми гранулами как в семенниках, так и в придатках наряду с неизменной дегрануляцией, что указывают на прохождение «подготовительной» фазы, заключающейся в миграции тучных клеток в репродуктивные органы и накоплении ими секрета. После следует начало активной дегрануляции, которая сопровождается возвращением количества тучных клеток к показателю интактной группы, сохранением повышенной синтетической активности и преобладанием в семенниках клеток со зрелыми гранулами. Более

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высокая доза ципрофлоксацина (400 мг/кг) ускоряет активацию тучных клеток, что приводит к более ранней дегрануляции. Количество и функциональные параметры тучных клеток под действием препарата изменяются аналогично в обоих исследуемых органах, однако наблюдаемые морфометрические изменения и показатели созревания гранул демонстрируют тканеспецифические адаптивные реакции. Проведенное исследование дает основание рекомендовать дозу 400 мг/кг в течение 7 дней для активации тучных клеток в репродуктивных органах самцов крыс и изучения сперматогенеза. Дозу 200 мг/кг следует использовать с целью предварительной стимуляции миграции тучных клеток, повышения их синтетической активности и созревания перед применением другого активатора – индуктора дегрануляции. Данная доза также будет предпочтительной для более длительных экспериментов, чтобы свести к минимуму потенциальные побочные эффекты, связанные с более высокой дозировкой.

Ключевые слова: тучные клетки, сперматогенез, дегрануляция, активация тучных клеток, ципрофлоксацин, семенник, придаток семенника

LONG-TERM ACTIVATION OF MAST CELLS AS AN EXPERIMENTAL MODEL FOR STUDYING THEIR ROLE IN THE REGULATION OF SPERMATOGENESIS

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Abstract. Mast cells are an important component of the immune microenvironment in the male reproductive system, involved in both physiological regulation and pathological processes via secretion of various bioactive substances. Modeling dysregulation through activation or inhibition of mast cells, and studying the impact of this disturbance on spermatogenesis, may help identify the precise regulatory mechanisms by which these cells influence this process. Ciprofloxacin, an antibiotic known to activate mast cells, has shown efficiency in cardiac mast cell studies but has not been investigated in spermatogenesis. The aim of this study was to evaluate the effects of various ciprofloxacin regimens on mast cells in reproductive organs of male Wistar rats and to determine an optimal dose and duration for developing a model suitable for investigating mast cell involvement in spermatogenesis. Male Wistar rats were treated with ciprofloxacin at 200 and 400 mg/kg for different durations. Morphological and functional characteristics of mast cells in the testes and epididymides were assessed histologically. Ciprofloxacin was shown to modulate the mast cell activity in a time-, dose-, and tissue- dependent manner. At a dose of 200 mg/kg for 7 days, it caused an increase in mast cell numbers, enhanced synthetic activity, and raised the proportion of cells with mature granules in both organs, while degranulation remained unchanged. This indicates a “preparatory” phase involving mast cell migration to reproductive tissues and granule accumulation. This process was followed by active degranulation after 14 days, associated with return to baseline cell numbers, sustained high synthetic activity, and a predominance of mast cells with mature granules, especially in testes. A higher ciprofloxacin dose (400 mg/kg) promoted acceleration of mast cell activation, leading to earlier degranulation. While functional changes were consistent across both organs, morphometric parameters and granule maturation showed tissue-specific responses. Notably, testicular mast cells displayed minimal morphometric changes, possibly due to the immune-privileged nature of the testes. Based on these findings, a 400 mg/kg dose for 7 days is recommended to induce mast cell activation for spermatogenesis studies. A 200 mg/kg ciprofloxacin dose is more suitable for pre-stimulation prior to the use of a degranulation inducer and for long-term studies, in order to minimize possible side effects associated with higher doses.

Keywords: mast cells, spermatogenesis, degranulation, mast cell activation, ciprofloxacin, testis, testis appendage

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Introduction

Mast cells (MCs) are an important component of the testicular microenvironment. Under normal conditions, they play a significant role in maintaining immune privilege and homeostasis within the testicular microenvironment [3]. This role is largely attributed to the regulatory effects of MC mediators on vascular permeability and immunomodulation. However, when MC function is impaired, these effects may shift towards a detrimental influence on spermatogenesis. Such dysregulation can disrupt the balance of the entire testicular microenvironment, potentially leading to various pathologies [8]. Modeling MC dysregulation, either through activation or inhibition, and examining its impact on spermatogenesis can help elucidate the precise mechanisms governing this process. While immunological factors play a significant role in MC activation, other various factors, including radiation, pathogens, proteins, proteolytic enzymes, opioids, estrogens, androgens, and certain antibiotics, can also trigger their response. Conversely, MC activity can be suppressed by low doses of γ-ionizing radiation (< 0.1 Gy), antihistamines, and MC stabilizers such as ketotifen [2]. Among antibiotics, fluoroquinolones which are effective against Gram-positive and Gram-negative bacteria, can also influence MC activity [6]. McNeil and colleagues reported that ciprofloxacin – the most used fluoroquinolone – can activate MCs via the Mas-related G-protein coupled receptor-X2 (MRGPRX2) [7], a detailed mechanism demonstrated by Liu et al. [5]. While ciprofloxacin has been used experimentally in studies of cardiac MCs [4], it has not been previously employed in studies of spermatogenesis, where longer-term activation is required due to the extended duration of the spermatogenic cycle.

The aim of this study is to evaluate the effects of different Ciprofloxacin administration regimens on MCs in the reproductive organs of male rats and to determine the optimal dosage and duration for developing a model to study the role of MCs in the regulation of spermatogenesis.

Materials and methods

The experimental animals were sexually mature male Wistar rats, aged 4 months, with a body weight of 350 – 472 g (n = 24). During the experiment, the animals were housed under standard vivarium conditions with a 12-hour light/dark cycle, without a special diet and with free access to drinking water. The study was approved by the Ethics Committee of the IIF UB RAS (No. 10-23, dated 09.10.2023).

All animals were divided into 4 groups: 1) a group of intact animals (INT), n = 6; 2) a group of animals receiving ciprofloxacin at a dose of 200 mg/kg/day for 7 days (C200D7), n = 6; 3) a group of animals receiving ciprofloxacin at a dose of 200 mg/kg/day for 14 days (C200D14), n = 6; 4) a group of animals receiving ciprofloxacin at a dose of 400 mg/kg/day for 7 days (C400D7), n = 6.

The animals were euthanized by ether overdose, and the testicles and epididymides were collected. Histological preparations were made and stained with toluidine blue to assess MC parameters, including their quantity and functional state. Additionally, alcian blue-safranin staining was used to evaluate the degree of MC granule maturity.

Preparation of drug suspension

A ciprofloxacin suspension was prepared by finely crushing two 250 mg ciprofloxacin tablets (Ozon, Russia) and dissolving them in 20 mL of water, resulting in a final concentration of 500 mg/20 mL. The required doses for each animal were calculated and administered via oral gavage. The suspension was thoroughly mixed before each administration to ensure uniform drug distribution.

Quantification of MCs density

Scans of prepared tissue sections were obtained using a Leica DM2500 light microscope (Leica, Germany) equipped with a Basler acA1920-40um camera (Basler, Germany) and the MultiMedia Catalog 2008-2020 software. The number of MCs was objectively quantified in all scans using QuPath 0.5.0 [1], and their density was calculated as the number of MCs per 1 mm^2 of tissue section.

Assessment of MCs synthetic activity

FIJI ImageJ 1.54f [9] was used to objectively assess MC synthetic activity. The software was calibrated using the Rodbard function to convert grayscale intensity values to optical density (OD). After calibration, all scans were converted to 8-bit grayscale. In each scan, the OD of 50 cells was measured; if fewer than 50 cells were present, all available cells were analyzed. A higher OD value indicates more intense MC synthetic activity.

Assessment of MCs functional activity

MCs were classified into four categories: inactive, weakly degranulating, moderately degranulating, and actively degranulating.

The degranulation index (DI) of MCs was calculated using the following formula:

$$DI = \frac{D}{D + I} \times 100\%,$$

where D – the number of MCs with clear signs of degranulation, I – the number of inactive MCs.

Assessment of MCs granule maturity

Using Alcian blue-safranin staining, MCs were classified into three groups:

– MCs with immature granules, stained blue due to the affinity of their components for Alcian blue alone (Alc+ granules);

– MCs with granules of intermediate maturity, stained purple due to the affinity of their components for both Alcian blue and safranin (Alc+ granules and Saf+ granules);

– MCs with mature granules, stained red due to the high content of heparin, a sulfated glycosaminoglycan with a strong affinity for safranin (Saf+ granules).

Evaluation of MCs morphometric parameters

Using FIJI ImageJ 1.54f, the area and perimeter of 50 cells were measured in each preparation. If fewer than 50 cells were present, all available cells were analyzed. The software was calibrated by capturing images of an objective micrometer with a known scale. The number of microns per pixel was determined by measuring the distance between marked divisions on the micrometer and inputting this value into the software to ensure accurate morphometric analysis.

Statistical analysis of the obtained data

All data were analyzed using GraphPad Prism 9.5.1. The Kruskal–Wallis test was used to compare the number of MCs, DI, and granule maturity between groups. Dunn's test for pairwise comparisons, with subsequent correction using the two-stage stepwise method of Benjamini, Krieger, and Yekutieli, was applied to accurately determine differences between independent groups.

One-way ANOVA was used to compare OD and morphometric parameters of MCs among three or more groups, followed by the Games–Howell post-hoc test to determine intergroup differences.

Differences were considered statistically significant at $p < 0.05$. Data in the tables are presented as M±SE, Me, and the 95% CI of the median.

Results and discussion

During the experiment, different dosages and administration durations of the drug were tested. Administration of ciprofloxacin at 200 mg/kg for 7 days led to an increase in the number of MCs in the testes and epididymides of rats, with most cells containing mature granules. An increase in their synthetic activity was observed, while functional activity remained unchanged (Table 1). These findings suggest that during the first week of administration, ciprofloxacin stimulates the migration of MCs to the reproductive organs, enhances their synthesis of bioactive substances, and promotes granule maturation. However, it does not affect MCs degranulation, which remains at the same level as intact animals.

After 14 days of ciprofloxacin administration at 200 mg/kg, the number of MCs in the testes and epididymides returns to normal. However, their synthetic activity remains elevated compared to MCs in intact animals. Unlike the first week, MCs degranulation in both the testes and epididymides increases significantly compared to the intact group and the C200D7 group (Table 1).

Administration of ciprofloxacin at 400 mg/kg for 7 days produces a combined effect similar to that of 200 mg/kg administered for 7 and 14 days. The number of MCs in the testes and epididymides increases significantly, accompanied by an increase in both synthetic and functional activity compared to the intact group (Table 1). In the testes, a large number of cells with mature granules are observed, whereas in the epididymis, there is only a tendency toward an increase in their number.

When comparing MCs parameters in the testes and epididymides, it was found that the number and functional activity of MCs changed similarly in both reproductive organs. However, synthetic activity, which generally increased with drug administration, and the distribution of cells based on granule maturity exhibited significant organ specificity. In the testes, synthetic activity showed a dose-dependent increase. In contrast, in the epididymides, synthetic activity decreased after two weeks of drug administration or when a higher dose of ciprofloxacin was used. This may suggest that testicular MCs replenish their granules more rapidly than epididymal MCs following degranulation. Additionally, in the testes, granule maturation was activated regardless of dose or duration of administration, whereas in the epididymides, this effect was observed only in the C200D7 group.

Morphometric characteristics of testicular MCs indicate greater resistance to the effects of ciprofloxacin, as their area remains unchanged compared to the intact group. A small, but significant, increase in their perimeter was observed after the administration of 200 mg/kg ciprofloxacin for two weeks and 400 mg/kg for one week, compared to the C200D7 group but remained at the same level as in the intact group. In contrast, epididymal MCs demonstrate a significant decrease in both area and perimeter following ciprofloxacin administration, regardless of the dose or duration.

The choice of drug doses in this study is based on the intravenous ciprofloxacin concentration of 150 mg/kg, which has been used in studies of cardiac MCs [4], where stable activation of these cells was demonstrated. According to the Northern Health (Canada) clinical guideline "Intravenous to oral conversion for antimicrobials" the ciprofloxacin conversion factor is 1.25. Therefore, an oral dose of 200 mg/kg was used in this study to activate MCs. To study the effect of an increased dose, a 400 mg/kg dosage (double the initial dose) was administered.

The results of this study demonstrate that ciprofloxacin modulates MCs activity in a time-, dose-, and tissue-dependent manner (Figure 1). The increase in the number and synthetic activity

TABLE 1. THE EFFECT OF CIPROFLOXACIN ON MAST CELL PARAMETERS IN THE REPRODUCTIVE ORGANS OF MALE RATS

Группы Groups	**Параметры** / Parameters							
	Количество ТК на 1 мм² среза, клеток/мм² MCs density, cells/mm²	**Синтетическая активность, ОП** Synthetic activity, OD	**Индекс дегрануляции, %** Degranulation index, %	**Площадь, мкм²** Area, μm²	**Периметр, мкм** Perimeter, μm	**ТК с разной степенью зрелости гранул, %** Maturation degree of MCs granules, %		
						Незрелые Immature	**Промежуточные** Intermediate	**Зрелые** Mature
Семенник / Testis								
ИНТ INT	0.32±0.04 0.30 (0.19-0.49)	0.319±0.005 0.330 (0.310-0.340)	48.65±8.82 49.45 (15.38-76.27)	38.87±1.56 36.00 (32.00-40.00)	25.71±0.47 25.35 (24.29-26.26)	16.99±0.72 16.67 (15.79-19.70)	23.07±6.56 23.07 (0.00-37.88)	59.95±6.88 59.95 (42.42-83.33)
Ц200Д7 C200D7	0.94±0.22[a] 0.90 (0.48-1.77)	0.492±0.005[d] 0.495 (0.484-0.503)	32.57±11.03 21.88 (9.23-66.67)	37.13±0.85 37.00 (34.00-39.00)	24.45±0.35 23.88 (23.31-24.97)	2.31±1.33[a] 1.28 (0.00-8.33)	2.26±1.45[a] 0.00 (0.00-7.69)	95.43±1.76[a] 95.59 (89.74-100.00)
Ц200Д14 C200D14	0.49±0.07 0.51 (0.19-0.68)	0.503±0.005[d] 0.511 (0.492-0.523)	73.00±4.88[b] 68.51 (61.90-93.75)	39.30±0.97 38.00 (35.00-40.00)	26.16±0.38[e] 25.89 (24.99-26.62)	0.91±0.58[a] 0.00 (0.00-3.03)	0.00±0.00[a] 0.00 (0.00-0.00)	99.09±0.58[a] 100.00 (96.97-100.00)
Ц400Д7 C400D7	0.93±0.18[a, c] 0.79 (0.57-1.80)	0.533±0.004[d, e, f] 0.534 (0.525-0.544)	77.61±2.31[a, b] 80.06 (67.80-82.00)	37.69±0.82 36.00 (35.00-38.00)	25.76±0.32[e] 25.34 (24.60-26.32)	0.75±0.34[a] 0.69 (0.00-1.69)	0.24±0.24[a] 0.00 (0.00-1.43)	99.01±0.49[a] 99.32 (97.14-100.00)
Придаток семенника / Epididymis								
ИНТ INT	2.45±0.37 2.04 (1.85-3.82)	0.389±0.004 0.390 (0.380-0.410)	54.95±5.59 55.56 (40.98-70.97)	64.05±2.29 56.00 (50.00-59.00)	31.67±0.52 30.50 (28.95-31.65)	33.11±6.53 30.23 (13.38-57.89)	14.47±2.70 12.15 (6.15-23.94)	52.42±5.63 46.51 (33.33-73.85)
Ц200Д7 C200D7	9.28±0.89[a] 8.96 (6.89-12.64)	0.534±0.004[d] 0.540 (0.530-0.550)	37.05±2.19 37.72 (27.47-43.08)	51.93±1.26[d] 49.00 (46.00-51.00)	28.43±0.34[d] 27.80 (26.97-28.72)	14.06±3.19 11.58 (6.14-27.47)	4.87±1.23[a] 4.95 (0.00-8.42)	81.08±3.66[a] 80.53 (67.03-91.11)
Ц200Д14 C200D14	4.11±0.59[b] 3.82 (2.72-6.31)	0.499±0.004[d, e] 0.510 (0.500-0.520)	71.92±2.61[b] 72.08 (62.00-80.49)	55.89±1.41[d] 51.50 (48.00-56.00)	29.60±0.36[d] 29.23 (28.02-30.10)	22.71±4.62 23.49 (8.72-34.52)	7.95±1.52 7.98 (2.68-13.75)	69.33±5.77 70.89 (52.50-83.89)
Ц400Д7 C400D7	6.21±1.50[a] 5.18 (2.63-11.94)	0.492±0.005[d, e] 0.490 (0.480-0.500)	77.43±3.15[a, b] 75.01 (70.18-91.18)	55.69±1.48[d] 51.00 (47.00-55.00)	29.66±0.38[d] 29.13 (28.16-29.95)	18.64±4.15 16.30 (7.32-35.62)	6.23±1.00[a] 6.78 (2.44-8.85)	75.14±4.80 78.48 (56.85-90.24)

Note. [a], differences are statistically significant compared to the corresponding parameter of the intact group according to the Kruskal–Wallis test, followed by Dunn's post-hoc test, with correction using the Benjamini, Krieger and Yekutieli method ($q < 0.05$). [b], differences are statistically significant compared to the corresponding parameter of C200D7 group according to the Kruskal–Wallis test, followed by Dunn's post-hoc test, with correction using the Benjamini, Krieger and Yekutieli method ($q < 0.05$). [c], differences are statistically significant compared to the corresponding parameter of C200D14 group according to the Kruskal–Wallis test, followed by Dunn's post-hoc test, with correction using the Benjamini, Krieger and Yekutieli method ($q < 0.05$). [d], differences are statistically significant compared to the corresponding parameter of the intact group according to one-way ANOVA with post-hoc test for multiple comparisons using the Games–Howell criterion ($p < 0.05$). [e], differences are statistically significant compared to the corresponding parameter of C200D7 group according to one-way ANOVA with post-hoc test for multiple comparisons using the Games–Howell criterion ($p < 0.05$). [f], differences are statistically significant compared to the corresponding parameter of C200D14 group according to one-way ANOVA with post-hoc test for multiple comparisons using the Games–Howell criterion ($p < 0.05$).

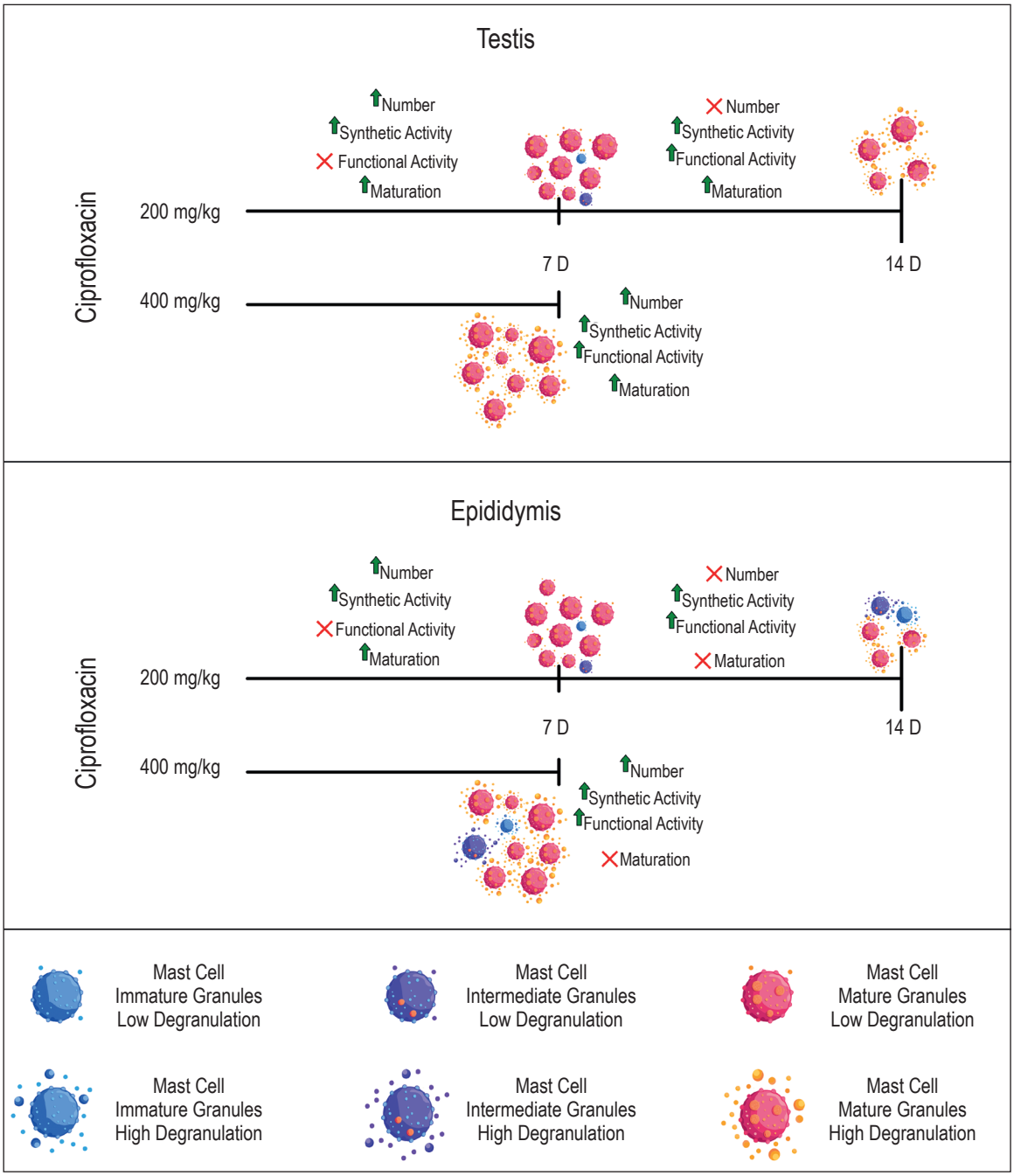

Figure 1. Effects of ciprofloxacin on mast cells with different intake regimens

of MCs, as well as the activation of their maturation in both the testes and epididymides, observed after administration of the drug at a dose of 200 mg/kg for 7 days, along with unchanged degranulation, suggests the transition through a "preparatory" phase of MCs, characterized by the migration of MCs into the reproductive organs and the accumulation of their secretion. This phase ends in the second week and is marked by the onset of active degranulation and the return of the MCs count to levels seen in the intact group, while synthetic activity remains elevated. Regulatory mechanisms may be involved, initially suppressing MCs degranulation, but eventually being eliminated due to prolonged drug-induced activation.

A higher dose of ciprofloxacin (400 mg/kg) accelerates MCs activation, resulting in earlier degranulation. This suggests that MCs response is influenced not only by time but also by dose.

While MCs parameters (quantity, synthetic and functional activity) change similarly in the testes and epididymides, the observed morphometric changes – specifically, the reduction in the size and altered shape of epididymal MCs – demonstrate tissue-specific adaptive responses. The absence of significant changes in the morphometric parameters of testicular MCs may be attributed to the unique immune-privileged microenvironment of the testes.

The conducted study provides grounds for recommending a dose of 400 mg/kg for 7 days to activate MCs in the reproductive organs of male rats and to study spermatogenesis. A dose of 200 mg/kg may be more suitable if the goal is to "prepare" MCs in the reproductive organs by stimulating their migration, synthetic activity, and maturation before applying another activator to induce degranulation. Additionally, this lower dose may be preferable for longer experiments to minimize potential side effects associated with higher dosages.

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