



Modeling experimental glaucoma for screening studies of antiglaucomatous activity

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Abstract

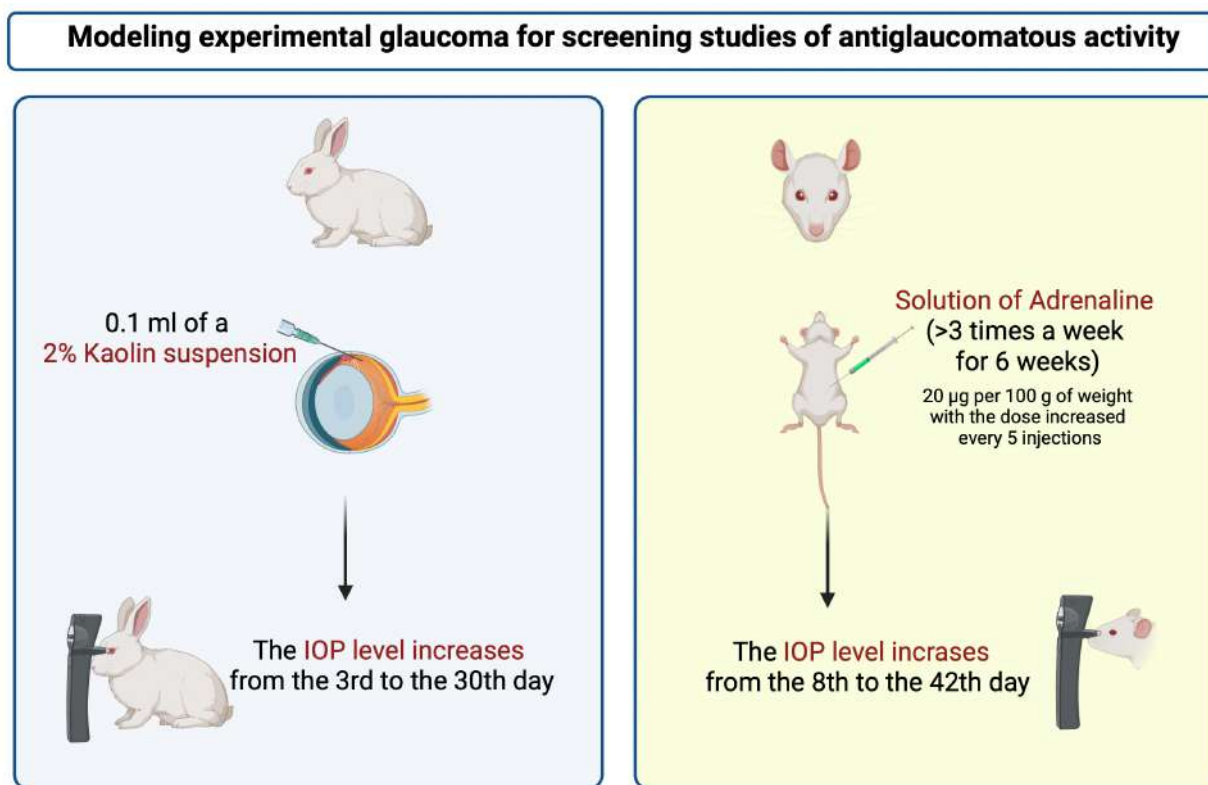
Introduction: *In vivo* screening studies, in which the efficacy of dozens of drugs is tested to select several applicants for further study of their safety in humans, are the main stage in the study of the pharmacodynamics of promising antiglaucoma drugs. This imposes a number of specific requirements both on experimental models of glaucoma and on laboratory animals used in the experiment.

Materials and Methods: 32 male rabbits of the Soviet Chinchilla breed, 6 male albino rabbits weighing 3-3.5 kg, and 20 outbred white rats weighing 220-250 g were used in total in experiments to reproduce the glaucoma process. All manipulations on the rabbit eye were performed by an ophthalmologist under general anesthesia with telazol. Triamcinolone (vitreal injection) was used to simulate glaucoma in rabbits, lauromacrogol 400 or fine kaolin (anterior chamber injection) was used to simulate glaucoma in rabbits; adrenaline hydrochloride (intraperitoneal administration) was used to simulate glaucoma in rats.

Results and Discussion: Double intravitreal administration of a suspension of triamcinolone at a dose of 4 mg was the most attractive model in terms of the technique of reproducing the pathology and the results obtained in modeling glaucoma in rabbits. However, this model did not produce a stable increase in intraocular pressure (IOP). Doubling the dose of triamcinolone and replacing chinchilla rabbits with albinos did not lead to a positive result. The introduction of the venous sclerosing drug lauromacrogol 400 into the anterior chamber of the eye proved to be ineffective either. The introduction of finely dispersed kaolin into the anterior chamber of the eye of rabbits led to a persistent increase in IOP. The intraperitoneal administration of epinephrine hydrochloride to rats according to the described method gave no stable results. The increase in IOP became stable only after a significant increase in the dose of adrenaline.

Conclusion: The conducted studies of four models of glaucoma and their three modifications in animals made it possible to select two of them, which contributed to a stable and fairly long-term increase in IOP in rabbits (introduction of finely dispersed kaolin into the anterior chamber of the eye) and rats (adrenaline-induced model).

Graphical Abstract



Keywords

glaucoma, intraocular pressure, experimental model of glaucoma

Introduction

The term “glaucoma” unites a large group of eye diseases (about 60) with the following features: intraocular pressure (IOP) exceeds the tolerable level constantly or periodically; a characteristic lesion of the optic nerve head and retinal ganglion cells develops (glaucoma optic neuropathy); characteristic visual disturbances occur (Al-Rajhi et al. 2020). This is a fairly common ophthalmic disease, which is the leading cause of irreversible blindness. According to the World Health Organization, the number of glaucoma patients in the world ranges from 60.5 to 105 million people, while the number of cases is predicted to increase by another 10 million over the next 10 years (Tham et al. 2014; Kuryshcheva 2020).

Glaucoma is classified as a multifactorial disease with a threshold effect. This means that a number of causes are necessary for the development of the disease, which together lead to its occurrence. Heredity, individual characteristics or anomalies in the structure of the eye, pathologies of the cardiovascular, nervous and endocrine systems are especially important. The emergence, development and progression of glaucoma is a sequence of risk factors that are summed up in their action, resulting in the triggering of a mechanism that leads to the onset of the disease. Thus, the pathogenesis of

glaucoma is complex and not fully understood, which ultimately determines the development of eye dysfunctions despite the treatment (Kuryshcheva 2020).

The basic concept in the treatment of glaucoma is the methodology for reducing intraocular pressure (IOP). This is the basis of therapy for open-angle glaucoma and part of a comprehensive treatment, including surgery, for closed-angle glaucoma. Medical therapy is the most common therapeutic practice for lowering IOP (Tham et al. 2014; Kuryshcheva 2020).

Thus, medical science faces two main tasks: an in-depth study of the pathogenesis of the disease and the search for effective ways to treat it. The solution of these problems is impossible without experimental studies on animals, the key element of which is the modeling of glaucoma. The use of experimental models of glaucoma makes it possible to expand knowledge about its pathogenesis, the development of glaucomatous optic neuropathy, the mechanism of drug action, and to search for new drugs.

This problem is solved by using various animals in the glaucoma simulation experiment – cows, sheep, monkeys, birds, freshwater fish, dogs, cats, pigs, guinea pigs, mice, rabbits, and rats (Bouhenni et al. 2012; Petrov et al. 2017).

Models of glaucoma reproduced in the experiment

can be divided into *in vitro* and *in vivo* models. The isolated retina or cultures of its individual cells (ganglionocytes, astrocytes, and microglial cells) are most often used for the *in vitro* modeling of glaucoma (Petrov et al. 2017; Izzotti et al. 2010). In this case, the glaucoma process is mimicked by increased pressure in the culture system, restriction of trophism and inhibition of the synthesis of ATP and cytochrome C oxidase, and initiation of excitotoxic damage (Alyabyeva et al. 2015).

In vivo models, however, do not lose their relevance, since they allow the most comprehensive and close-to-the-clinical picture to reproduce the course of the pathological process. They are divided into models of glaucoma itself, based on an increase in IOP, and models of neuropathy, not dependent on changes in ophthalmotonus (Gazizova et al. 2013).

The modeling of diseases and pathological conditions becomes especially important in the development of new drugs. *In silico* (computer modeling of processes) and *in vitro* (inhibition activity of certain enzymes or interaction with receptor-membrane complexes) methods make it possible to screen out at least 90% of the synthesized compounds, and from the rest – to carry out a primary selection of the most promising candidates, which range from several dozen to several hundreds. However, the final decision concerning a new compound remains with the *in vivo* model experiment. Glaucoma is no exception to this rule (Gazizova et al. 2013; Petrov et al. 2017).

The main stage in the study of the pharmacodynamics of promising antiglaucoma drugs are *in vivo* screening studies in which the effectiveness of dozens of drugs is tested to select several applicants for further studies on their safety for humans. This imposes a number of specific requirements both on experimental models of glaucoma and on laboratory animals used in the experiment.

Since the work requires a large number of laboratory animals, they must be available, their care must be simple, and the procedure for monitoring IOP must be simple with the minimum required equipment. It is preferable to use rats (as rodents) and rabbits (as non-rodents). The similarity of the anatomical structure of the anterior chamber angle in rats and humans is one of the reasons for this choice (Daimofl et al. 1997). The main mechanism for the outflow of aqueous humor in rats, as in primates, is through the trabecular meshwork into the Schlemm canal, then into the limbal plexus, and into the episcleral veins. The characteristic symptoms of the disease when modeling glaucoma in rats are very similar to those in humans (Morrison et al. 1995; Gazizova et al. 2013).

The model of experimental glaucoma, on the one hand, should adequately reproduce the pathological processes that occur in humans (increase in IOP, first of all), and on the other hand, should be easy and well reproduced.

Aim of work: to select models of glaucoma in rabbits and rats suitable for screening drugs for antiglaucomatous activity, guided by literature data.

Materials and Methods

Animals

32 male rabbits of the Soviet Chinchilla breed, 6 male albino rabbits weighing 3-3.5 kg, 20 outbred white rats weighing 220-250 g were used in total in experiments to

reproduce the glaucoma process. All manipulations on the rabbit eye were performed by an ophthalmologist under general anesthesia with telazol. IOP of rabbits was determined using an Icare TonoVet veterinary blood pressure monitor designed for use with small pets. The experimental studies were approved by the Bioethical Commission of Yaroslavl State Pedagogical University named after K.D. Ushinsky (Minutes 63 of 23 June 2023).

Modeling glaucoma

Corticosteroid model of glaucoma. An analysis of the scientific literature on the modeling of glaucoma in rabbits (Bouhenni et al. 2012; Gazizova et al. 2013; Alyabyeva et al. 2015) showed that the corticosteroid model of the disease is technically the simplest and relatively less laborious (Jones and Rhee 2006; Kersey and Broadway 2006). One of its most modern variants is the double administration of a suspension of **triamcinolone** at a dose of 4 mg (injection volume of 0.1 ml) into the vitreous body of the eye. Re-introduction of **triamcinolone** is carried out 7 days later. The development of persistent ophthalmohypertension on days 7-14 of the experiment is described in publications. The duration of ophthalmohypertension lasted at least a month (Song et al. 2011). Modification applied: **triamcinolone** (4 mg intravitreally) was administered 2 times a week for 2 weeks.

The use of venosclerotic drugs

Violation of the outflow of blood from the eye through the venous bed is one of the ways to model glaucoma in animals (Aznabaev et al. 1998). Six male rabbits of the Soviet Chinchilla breed were injected with 0.1 ml (2 mg) lauromacrogol 400 once into the anterior chamber of the eye for this purpose. The development of a persistent increase in IOP occurred on the 3rd day.

The mechanism of modeling glaucoma with the introduction of **finely dispersed kaolin** into the anterior chamber of the rabbit eye is based on a violation of the outflow of intraocular fluid from it (Prigogina 1996). 6 male rabbits of the Soviet Chinchilla breed were injected with 0.1 ml of a 2% suspension (2 mg) of finely dispersed kaolin into the anterior chamber of the eye once for this purpose.

Adrenaline model of glaucoma in rats

A solution of adrenaline was administered to 10 white male rats weighing 220-250 g intraperitoneally at a dose starting from 10 µg, increasing to 15 µg per 100 g of body weight. 20 injections over 6 weeks, an average of 3 injections per week, were given in the experiment. The dose of injected adrenaline was increased every 5 injections. IOP during adrenaline induction was measured prior to injections (Mikheyteva 2014). Applied modification: doubling the initial dose of administered adrenaline followed by a 1.5-time dose increase every week until a persistent increase in IOP is recorded.

Statistical analysis

All calculations were made using the computer program BIostatistics. The number of determinations of each indicator in different experiments ranged from 6 to 10. Student's t-test (in the presence of a normal distribution) and the nonparametric Wilcoxon test (in its absence) were

used for intergroup comparisons; Student's t-test with Bonferroni correction was used for multiple comparisons. Significance of intragroup differences was determined using paired Student's t-test. Differences were considered significant at $p < 0.05$.

Results and Discussion

The most attractive model in terms of the technique of pathology reproduction and the results obtained in modeling glaucoma in rabbits was a double intravitreal injection of a suspension of triamcinolone at a dose of 4 mg (volume of 0.1 ml). In total, 12 male rabbits of the Soviet Chinchilla breed were involved in this experiment. Glucocorticoid was injected into the right eye; the left eye was the control. The averaged data of the first series of the experiment are shown in Table 1.

The conducted studies have shown that it was not possible to obtain a stable increase in IOP in rabbits with a twofold injection of triamcinolone (once a week) into the vitreous body. IOP in intact rabbits ranged from 11–17 mm Hg, only in 3 animals IOP was above 20 mm Hg (21–35 mm Hg) after the second injection of triamcinolone on the 14–21st days of the experiment, and then returned to normal within 3–6 days. The maximum mean IOP value rose unreliably from the initial 14.1 ± 0.6 mm Hg to 18.3 ± 2.7 mm Hg on the 21st day of the experiment ($p > 0.05$).

Since many sources describe the preferred use of albino rabbits for modeling glaucoma, it was decided to conduct the next series of experiments on them. The results obtained on albino rabbits did not fundamentally differ from those obtained on Soviet Chinchilla rabbits, as can be seen from Table 1. IOP in only one animal out of six on the 14th day of the experiment increased to 32 mm Hg (from the initial 15 mm Hg), but by the 21st day it had decreased to 19 mm Hg.

Thus, an attempt to reproduce the “classical” corticosteroid model of glaucoma in rabbits described in the literature using a double intravitreal injection of triamcinolone suspension, on the one hand, was considered unsuccessful, and, on the other hand, a significant increase in IOP was still obtained in 25% of rabbits of the

Soviet Chinchilla breed. The decision to double the dose of triamcinolone by increasing the frequency of administration of the drug up to 4 times (2 times a week) was made on the basis of these data. It was not possible to increase the volume of administered contents (single dose) due to possible damage to the vitreous body.

However, a 2-fold increase in the dose and frequency of administration of triamcinolone did not lead to any significant results: only 3 rabbits out of 8 (37.5%) showed a significant increase in IOP, and in one of them it once reached 20 mm Hg, the other two went up to 28 mm Hg (up to 3 days) and 33 mm Hg (up to 5 days). An attempt to model glaucoma by administering a suspension of triamcinolone was deemed unsuccessful based on the data obtained.

Another technically simple method for modeling glaucoma in rabbits is the introduction of venosclerotic agents into their anterior chamber of the eye. Violation of the outflow of blood from the eye through the venous bed is one of the ways to increase IOP in animals. According to, 0.1–0.3–0.5 ml of a venous sclerosing drug was injected into the anterior chamber of the eye of rabbits; the optimal effect was achieved with an injection volume of 0.3 ml. A persistent increase in IOP in rabbits began on days 3–4 and formed over the next 3–4 days after the introduction of a venosclerotic agent into the anterior chamber of the eye.

Six male rabbits of the Soviet chinchilla breed were given a single dose of 0.2 ml (4 mg) lauromacrogol 400 (ethoxysclerol) into the anterior chamber of the eye to simulate ophthalmohypertension. The results of this experiment are presented in Table 2. The level of IOP more than 20 mm Hg (22 mm Hg and 24 mm Hg) was registered only in two out of six rabbits on the 3rd day after the administration of ethoxysclerol. The level of IOP in these rabbits returned to normal on days 4 and 5. Moreover, an infectious lesion of the experimental eye developed in half of the studied rabbits despite the aseptic conditions for the introduction of the drug into the eye and subsequent antimicrobial measures. Irreversible changes in the structures of the eye were observed in 100% of cases. This attempt to model glaucoma was considered unsuccessful.

Table 1. Modeling glaucoma in rabbits: intravitreal administration of triamcinolone

A series of experiments	N	Eye	Initial IOP	Day 4	Day 7	Day 11	Day 14	Day 21	Day 28	Day 35
Rabbits of the Soviet Chinchilla breed: 2-fold introduction	12	C	13.5±0.6	12.8±0.7	13.0±0.5	13.6±0.9	14.2±1.0	13.8±0.8	13.2±0.5	12.6±0.7
		E	14.1±0.6	13.5±0.9	14.8±1.2	14.6±1.1	16.8±2.9	18.3±2.7	14.9±1.8	14.0±0.9
Albino Rabbits: 2-fold introduction	6	C	14.5±0.9	14.8±0.8	13.9±0.7	14.4±0.6	14.5±0.9	14.0±0.8	13.8±0.7	14.0±0.9
		E	14.0±0.7	13.2±0.6	13.0±0.9	14.5±1.3	15.6±3.2	14.9±2.3	14.1±0.9	13.6±1.2
Rabbits of the Soviet Chinchilla breed: 4-fold introduction	8	C	12.8±0.7	13.0±0.8	13.2±0.9	13.3±0.9	14.2±1.0	13.8±0.8	13.2±0.5	12.6±0.7
		E	13.2±0.6	12.1±1.0	14.2±1.0	14.9±1.3	17.9±3.1	15.3±2.0	13.8±1.1	12.4±1.1

Note: IOP – intraocular pressure; C – control eye; E – experienced eye. * – significant difference from baseline.

Table 2. Modeling glaucoma in rabbits: injection of ethoxysclerol into the anterior

A series of experiments	N	Eye	Initial IOP	Day 2	Day 3	Day 4	Day 5	Day 7	Day 10	Day 14
Chinchilla Rabbits: Single Introduction	6	C	15.0±0.9	14.8±1.1	14.0±0.9	14.4±0.9	14.1±0.8	13.9±0.9	14.2±0.7	14.6±0.9
		E	14.8±0.7	15.5±1.5	17.1±2.5	16.7±1.9	14.6±1.1	13.3±1.2	13.9±1.1	14.0±0.8

Note: IOP – intraocular pressure; C – control eye; E – experienced eye; * – significant difference from baseline.

The mechanism of modeling glaucoma with the introduction of finely dispersed kaolin into the anterior chamber of the rabbit eye is based on a violation of the outflow of intraocular fluid from it (Prigogina 1966). It is believed that the disadvantage of this method is the resorption of kaolin after 1-2 months and the decrease in IOP 2-3 months later.

Six male rabbits of the Soviet Chinchilla breed were injected with 0.1 ml of a 2% suspension (2 mg) of finely

dispersed kaolin into the anterior chamber of the eye to reproduce this model of experimental glaucoma. The results of the experiment are presented in Table 3. The level of IOP significantly and steadily increased in the experimental eye from the 3rd to the 30th day after the introduction of kaolin in this series of experiments. An increase in IOP over 20 mm Hg (22-52 mm Hg at different times of the experiment) was observed in 5 out of 6 animals.

Table 3. Modeling glaucoma in rabbits: injection of kaolin into the anterior chamber of the eye

A series of experiments	N	Eye	Initial IOP	Day 3	Day 7	Day 10	Day 15	Day 20	Day 30
Chinchilla Rabbits: Single Introduction	6	C	14.0±1.1	14.7±1.3	13.7±0.9	14.7±1.3	13.0±0.4	17.0±1.1	13.7±0.9
		E	12.0±0.7	14.5±0.7*	29.7±6.3*	31.7±6.4*	27.0±5.5*	28.0±6.2*	20.3±5.4

Note: IOP – intraocular pressure; C – control eye; E – experienced eye; * – significant difference from baseline.

Thus, stable ophthalmic hypertension lasting up to a month developed in most animals after the administration of kaolin. This makes it possible to use this particular model of the glaucoma process in rabbits for screening the therapeutic activity of promising antiglaucoma agents.

Modeling human diseases on small laboratory animals is a common phenomenon that allows, on the one hand, to reduce the cost of research, and, on the other hand, to increase the amount of experimental material. Modeling glaucoma in rats is no exception to this rule (Livne-Bar et al. 2012; Petrov et al. 2017).

Adrenaline-induced glaucoma in rats is considered an adequate model of the human glaucoma process and is reproduced by fractional administration of adrenaline over a certain period of time (Mikheyteva 2014). The choice of the model of adrenaline-induced glaucoma is

due to the formation of a characteristic symptom complex of the glaucoma process: increased IOP, degenerative changes in the trabecular zone of the anterior chamber angle, degeneration of retinal ganglion cells, and specific atrophy of the optic nerve (Gazizova et al. 2013).

A solution of adrenaline was administered intraperitoneally to 10 white male rats weighing 220-250 g. The introduction started with a dose of 10 µg, with the dose increased every 5 injections, bringing it up to 15 µg per 100 g of weight. There were 20 injections over 6 weeks, with an average of 3 injections per week. The results of the experiments are presented in Table 4. A significant increase in IOP was observed sporadically only on days 8 and 36 of adrenaline administration (by 26% and 16%, respectively) and only in the right eye.

Table 4. Modeling of epinephrine-induced glaucoma in rats

A series of experiments	N	Eye	Initial IOP	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
Recommended dose of adrenaline according to the method	10	L	10.8±0.9	11.3±0.6	10.0±0.6	10.7±0.6	9.9±1.1	10.0±0.4	8.7±0.7
		R	9.7±0.4	12.3±0.9*	11.2±0.8	10.0±0.7	9.9±0.7	9.7±0.7	8.8±0.7
The dose of adrenaline was initially increased twice	10	L	8.0±0.4	10.3±0.9*	11.0±0.6*	10.5±0.7*	11.5±1.1*	12.8±0.6*	11.3±1.1*
		R	8.5±0.6	11.5±1.3*	11.2±1.1*	11.2±0.6*	10.0±1.5	12.3±1.0*	10.5±1.9

Note: IOP – intraocular pressure; L – left eye; R – right eye; * – significant difference from baseline.

These data served as the basis for a twofold increase in the dose of injected adrenaline at the beginning of the experiment and its further 1.5-time increase every week until a persistent increase in IOP was recorded, after which the dose of the injected drug stabilized; adrenaline was administered until the end of the experiment at this established dosage. Changing the dosage of adrenaline significantly changed the modeling process: there was a stable increase in IOP in both eyes from the 8th day of the experiment and during the next 6 weeks of the experiment. The increase in IOP was +29-60% in the left eye and +40-45% in the right eye.

Conclusion

The conducted studies of four models of glaucoma and their three modifications in animals made it possible to

select two of them, which contributed to a stable and fairly long-term increase in IOP in rabbits (introduction of finely dispersed kaolin into the anterior chamber of the eye) and rats (adrenaline-induced model).

Conflict of interests

The authors have no conflict of interests to declare.

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