ANIMAL MODELS IN THE STUDY OF THE GLAUCOMA: PAST, PRESENT AND FUTURE

MODELOS ANIMALES EN EL ESTUDIO DEL GLAUCOMA: PASADO, PRESENTE Y FUTURO

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Studies made with animal models have assisted in understanding the mechanisms of formation and evacuation of the aqueous humor as well as homeostasis maintenance of intra-ocular pressure. Frequently, this type of study leads to a knowledge about the etiology of glaucoma and the development of therapies. Through the diversity of structures and the function of drainage angles specific to each animal species, compared studies have broadened otherwise limited concepts about the human anterior segment disease. Due to their contribution to knowledge about hyper-tension and spontaneous or induced glaucoma, animal models have facilitated the development of therapeutic strategies which could not have been developed otherwise.

A variety of spontaneous glaucoma models have been described in different animal species. In the early sixties, Kolker’s group described a group of albino New Zealand rabbits which spontaneously exhibited an alteration in the development of the trabecular mesh (1). The anatomic description of these alterations – a reduction in the number of lamelles, increased inter-cellular spaces between lamelles, vacuolation of the endothelial cells and fragmentation of the basal cell – gave ground to the hypothesis that the cause of elevated intra-ocular pressure could be a reduction in the structural support of the trabecula. In addition, high fibrin levels were detected in the aqueous humor, suggesting that this fibrin could obstruct the evacuation thereof and therefore raise intra-ocular pressure. However, the absence of the lamina cribosa and the partial myelinization of the retina ganglionary cells, together with the existence of a prominent vascular sac, have made the rabbit an inadequate animal model for studying alterations in the retina or its vascularization in glaucoma.

In the late sixties, the observations by veterinary ophthalmologists lead to the description of dogs with spontaneous glaucoma, discovering the existence of some races (Beagles, Cokers and Basset Hounds) which are more sensitive to said pathology. But while in the case of rabbits, the type of glaucoma is open angle, with dogs its closed angle glaucoma. The Cocker race develops glaucoma since an early age, whereas with Beagles and Bassets the process is progressive and is expressed between 6 and 12 months of age (2). In Beagles it is a simple recessive autosomal inheritance and the pre-glaucoma stage is identified by an increase of intra-ocular pressure, with gonioscopy revealing an open angle without other abnormalities. However, when the glaucoma develops, the angle begins to close after 2-3 years. Chronic pressures of 30 - 40 mmHg can have transient peaks of up to 60 - 80 mmHg, inducing the excavation of the optic nerve head. In these animals, glaucoma can be treated pharmacologically with a number of drugs utilized in humans, with pilocarpine, epinephrine, acetazolamide and dichlorphenamide being effective for that purpose.

In 1993 the first description was published about a group of Macaca monkeys, located in quay Santiago. In nine families of these monkeys a maternal inheritance was found with a prevalence of 40% of increased intra-ocular pressure. Affected animals exhibited a loss of retina ganglionary cells, excava-

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tion of the optic nerve and electro physiological evidence of damages in the retina peripheral field (3).

Recently, the appearance of the DBA/2J mouse, which develops a progressive increase of intra-ocular pressure which induces the death of ganglionary cells (4) has given rise to a large amount of studies to establish the existence of homologies with some type of glaucoma in humans. The increase in intra-ocular pressure in these animals appears at 8 months of age and the pressure remains chronically high until their death. However, some factors such as the reduced size of the ocular globe or the absence of lamina cribosa limit the use of these animals of some types of studies.

These animal models of spontaneous chronic high intra-ocular pressure are suited for studying the causes of this pathology. However, with the exception of the DBA/2J mice, animals with spontaneous glaucoma are difficult to obtain in the market and even more to obtain groups with a similar stage of the pathology. Therefore and in order to facilitate experimentation and progress of our knowledge about glaucoma, throughout history experimental models of induced glaucoma have been developed.

In some cases, the induction of experimental glaucoma was prior to the description of a spontaneous glaucoma model, as in the case of the development of the glaucoma model with laser in primates. Thus, in 1974 Gaasterland et al developed the first model of laser in primates, which was subsequently broadly used by other authors. Just like in humans, after a trabeculoplasty with argon laser, a temporary increase in intra-ocular pressure occurs, which seems to be caused by the formation of fibrin meshes obstructing the spaces of the trabecular mesh. However, in all models of primate glaucoma following this procedure, a fixed midriasis occurs probably due to the damage suffered by the ciliar nerves. In addition, large fluctuations take place in the intra-ocular pressures and, in most cases, several laser sessions are needed to obtain continuous high pressure. This causes severe inflammations in the ocular globe and trabecular alterations which preclude pharmacological studies in this region. Regardless of these difficulties in the experimental glaucoma field, primates have been broadly used for improving clinical indicators of initial optic nerve damages in glaucoma.

In the viewpoint of the undersigned, the main progress in the study of glaucoma was driven by the development of glaucoma models in rats. These animals are much more economic and easier to maintain, apart from giving rise to much smaller ethical issues. In 1995, the group of Dr. Sharma developed the cauterization of epi-scleral veins in rats as a model for obtaining chronically high intra-ocular pressures (5). This model protects the trabecula structure and does not affect the ciliar nerve as is the case of the laser model. In addition, intra-ocular pressure can be kept high for up to 6 months which represents 25% of a rat’s life. The development of this animal model has allowed pharmacological trials of different combinations and concentrations of pressure-reducing and neuron-protecting drugs as an initial stage for subsequent study in larger animals prior to clinical trials in humans. In this case, rats are making a great contribution to anti-glaucoma study.

In the above mentioned year, the same group of Dr. Sharma also described for the first time the death of retina ganglionary cells following a pattern or program known as apoptosis (6). This pattern involves molecules known as caspases which, when inhibited at a certain time of the damage-inducing process, rescue cells from death, thus providing them neuro-protection. Even though the rat is an animal model which can be used in high numbers in order to carry out pharmacological tests, the size of its eye limits its use in some areas of ophthalmology. For this reason, our research group developed a glaucoma model in pigs and mini-pigs, utilizing the same epi-scleral cauterization system (7). This has allowed us to carry out vascular and retinal studies utilizing the same technology used in human ophthalmology.

Progress in glaucoma treatment has been associated to the development of animal models, just like progress in the diagnostic of glaucoma has gone hand in hand with technological developments. Let us hope that in the next few years we will be able to take advantage of an exponential progress in the prevention and neurological protection of glaucoma, utilizing the animal model developed in the past few years.

REFERENCES

Animal models in the study of glaucoma: past, present and future


