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Editorial

The Need for Relevant Functional Endpoints in Ophthalmic Drug Discovery

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Introduction

The costs for bringing a drug to market are rising exponentially, and estimates are putting an average price tag of somewhere between $500 million and $5 billion on any single new drug [1,2]. These increases are seen at all phases of drug development, i.e. drug discovery, preclinical studies in experimental models, and human clinical trials [3]. At the same time, new genomic and combinatorial chemistry approaches have dramatically increased the number of drug candidates, requiring new high-throughput and high-content technologies for hit discovery and early preclinical development, further increasing drug development costs [3].

The cost of drug development is further driven by poor success rates of taking drug candidates through clinical trials. According to a recent study, only less than 20% of self-originated drugs received FDA approval during the period from 1993 to 2009 [4]. The same study reported significant differences between small molecules (13% approval rate) and large molecules (32% approval rate) [4].

In Ophthalmology, only 21 ocular drugs received FDA approval in the last ten years, including ophthalmic reformulations of previously approved active compounds. This is contrasted by a critical need for both new and complementary therapies for a number of ocular diseases with a significant financial and societal impact, including glaucoma, diabetic retinopathy and age-related macular degeneration. With age being a major risk factor for all of these diseases, prevalence rates are predicted to rise significantly over the next decade.

In order to reduce the costs of drug development and to increase approval rates, research efforts have to focus on utilizing a comprehensive arsenal of relevant functional endpoints to help predict a drug's efficacy. While appropriate technologies and commercial solutions exist, many of these functional endpoints are not routinely utilized in ophthalmic drug discovery and vision research. Especially academic laboratories with an interest in drug discovery have failed to endorse the technologies, largely due to diminishing federal research budgets, but also due to unwillingness to contract with a clinical research organization with the appropriate expertise. As a result, many promising drug targets and drug candidates never enter the drug development phase.

In the following, we will briefly describe some relevant functional endpoint for ophthalmic drug discovery.

Optokinetic measurements of functional vision

Progressive vision loss is a significant clinical presentation for many ocular diseases, such as glaucoma. Vision loss occurs in normotensive glaucoma, and also continues to occur despite therapeutic control of the intraocular pressure in hypertensive glaucoma [5]. However, only very few laboratory studies in preclinical glaucoma models test the effect of drug candidates on functional vision in rodents. This is in light of the fact that multiple systems have been described that utilizes the optomotor reflex to assess visual acuity and contrast sensitivity [6-8]. The OptoMetry™ system (Cerebral Mechanics, Lethbridge, AB) relies on the natural optokinetic tracking response, which is a correlate of visual acuity [8]. Testing can be performed also by altering the contrast of the grating permitting the determination of the contrast sensitivity threshold. The asymmetry of the optokinetic motor reflex allows testing visual function separately for each eye, using a clockwise grating direction to measure visual acuity in the left eye and a counterclockwise grating direction for measurement in the right eye [9]. We have previously characterized the progressive loss of visual acuity and contrast sensitivity in the DBA/2J mouse model for human pigmentary glaucoma [10]. Similarly, the reduction in optokinetic response-determined visual acuity correlated with IOP increases in the microbead model [11]. Similar systems relying on optokinetic tracking have been reported [6,7], and shown loss of vision in albino CD1 and rd1 retinal degeneration mice [7]. Last year, the Kretzberg lab published a paper describing the first fully automated measurement and stimulation system to determine mouse visual thresholds based on optomotor responses (OMR-Arena) [6]. Most importantly, the optomotor response has been shown to improve after pharmaceutical intervention in a model of neuronal ceroid lipofuscinosis [12].

In summary, quantifying visual acuity in rodents is a feasible approach and important functional endpoint to test the effect of drugs and drug candidates in preclinical models.

Electrophysiological characterization of vision as functional endpoint

The light induces electrical activity in the eye, which can be recorded by electroretinography. Electroretinogram (ERG) responses can be recorded non-invasively using an electrode positioned on the cornea. Distinct components of the ERG response correspond to the function of specific retinal cell types. For example, the a-wave of the ERG is generated by photoreceptors, the following b-wave represents mixed electric responses from photoreceptors, interneurons and retinal glia, and the c-wave is known to originate from the retinal pigment epithelium [13]. The function of photoreceptors, rods and cones, can be differentiated depending on the adaptation status of the eye to light. ERG recorded from dark-adapted eyes reflects function

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of rod photoreceptors, whereas ERG performed on light-adapted eyes shows the activity of cones [13]. Functional integrity of retinal ganglion cells (RGCs) can be monitored by pattern ERG (PERG) [14]. This recording method eliminates signals from a- and b-waves by introducing reversal of the contrast of a grating pattern on the screen under light-adapted conditions, which produces non-linear signals from RGCs (for review, see [15]). ERG is thus overall a valuable and efficient tool to diagnose retinal degeneration as occurs in retinitis pigmentosa, Leber's congenital amaurosis, and glaucoma.

In preclinical drug testing, however, an even more comprehensive description of the functional integrity of the visual system can be obtained by intracortical recording of visual evoked potentials (VEPs). Chronically implanted electrodes into monocular sites of the primary visual cortex sense the visual information collected and processed in the retina and sent through visual tracts to the brain. In contrast to ERG, which provides information about the local response of retinal cells from the eye, VEPs allow to evaluate the functional integrity of optic tracts as well [16]. In neurodegenerative diseases such as glaucoma, where the pathophysiology of the disease is directly correlated with damage to the optic nerve head, the functional characterization of visual function using VEPs provides superior and more accurate data than those obtained by PERG or ERG alone. Furthermore, it should be mentioned that it is possible to record ERG and VEP responses simultaneously, thereby maximizing the information that can be obtained from a single eye.

To conclude, the electrophysiological characterization of the visual system using either ERG or VEPs, or in some cases both at the same time, becomes a necessity for preclinical studies aiming at new treatment modalities for neurodegenerative diseases.

Conclusion

Commercial technologies exist to test ocular drug candidates using relevant functional endpoints that can comprehensively assess the function of the visual system. Especially in academic preclinical research, we can no longer afford to ignore methodologies, such as optokinetic measurements, ERG and PERG, and VEP measurements; the cost associated with drug development and the success rates of clinical trials can only be improved if we utilize relevant functional endpoints as early as possible in the drug development pipeline.

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