Experimental Eye Research xxx (2016) 1–18

Contents lists available at ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

Review

Unconventional aqueous humor outflow: A review

Mark Johnson [a, b, c, *], Jay W. McLaren [d], Darryl R. Overby [e]

[a] Department of Biomedical Engineering, Northwestern University, Evanston, IL, USA
[b] Department of Mechanical Engineering, Northwestern University, Evanston, IL, USA
[c] Department of Ophthalmology, Northwestern University, Chicago, IL, USA
[d] Department of Ophthalmology, Mayo Clinic, Rochester, MN, USA
[e] Department of Bioengineering, Imperial College London, London, England, UK

ARTICLE INFO

Article history:
Received 17 September 2015
Received in revised form
4 January 2016
Accepted in revised form 26 January 2016
Available online xxx

Keywords:
Aqueous humor dynamics
Trabecular
Uveoscleral
Uveovortex
Mouse
Primate
Tracers
Indirect

ABSTRACT

Aqueous humor flows out of the eye primarily through the conventional outflow pathway that includes the trabecular meshwork and Schlemm's canal. However, a fraction of aqueous humor passes through an alternative or 'unconventional' route that includes the ciliary muscle, supraciliary and suprachoroidal spaces. From there, unconventional outflow may drain through two pathways: a uveoscleral pathway where aqueous drains across the sclera to be resorbed by orbital vessels, and a uveovortex pathway where aqueous humor enters the choroid to drain through the vortex veins. We review the anatomy, physiology and pharmacology of these pathways. We also discuss methods to determine unconventional outflow rate, including direct techniques that use radioactive or fluorescent tracers recovered from tissues in the unconventional pathway and indirect methods that estimate unconventional outflow based on total outflow over a range of pressures. Indirect methods are subject to a number of assumptions and generally give poor agreement with tracer measurements. We review the variety of animal models that have been used to study conventional and unconventional outflow. The mouse appears to be a promising model because it captures several aspects of conventional and unconventional outflow dynamics common to humans, although questions remain regarding the magnitude of unconventional outflow in mice. Finally, we review future directions. There is a clear need to develop improved methods for measuring unconventional outflow in both animals and humans.

Contents

* Corresponding author. Department of Biomedical Engineering, Northwestern University, Evanston, IL, USA.
E-mail address: m-johnson2@northwestern.edu (M. Johnson).

http://dx.doi.org/10.1016/j.exer.2016.01.017
0014-4835/

1. Introduction

The pathway of aqueous humor drainage has long been of interest and is of great importance because it provides the fluid resistance that maintains a proper intraocular pressure (IOP). IOP that is too low can impair vision by distorting the retina, cornea, and lens; IOP that is too high can lead to glaucomatous optic neuropathy.

Aqueous humor drainage from the anterior chamber through the trabecular meshwork, Schlemm's canal, collector channels, aqueous veins, and into the episcleral veins was first proposed by Leber (1873), Schwalbe (1870), and Knies (1875), and finally demonstrated by Seidel (1921) and Ascher (1942). The latter's observations of clear fluid in aqueous veins established this path as the primary route of aqueous humor outflow from the eye. After exploring aqueous humor drainage in more detail by using tracer molecules, investigators eventually realized that aqueous humor also left the eye through another route, passing through the uvea, the ciliary body and muscle, and into the choroid and sclera. This pathway has been called the uveoscleral, uveovortex, or unconventional pathway to distinguish it from the trabecular pathway, and has been estimated to carry 3–82% of the total aqueous humor outflow in different species. This paper will review the historical basis of our understanding of unconventional outflow, its properties and characteristics, how it is measured, and its significance to glaucoma research.

2. Historical basis of unconventional outflow

Leber reported in 1903 that tracers introduced into the anterior chamber passed not only into the conventional trabecular outflow pathway but also were found in the suprachoroidal space (Nesterov, 1986). Other early investigators (Nuel and Benoit, 1900; Erdmann, 1907; Seidel, 1921; Kiss, 1943) reported that colloidal tracer accumulated outside the conventional outflow pathway, often deep within the peripheral ciliary body, posterior sclera, and choroid after perfusion with these tracers. These studies led investigators to infer the existence of a secondary aqueous humor outflow pathway (Fine, 1964) now known as the “unconventional” outflow pathway.

It was not until studies in monkeys by Anders Bill and colleagues in the 1960's that our functional understanding of unconventional outflow solidified. Bill explored this pathway quantitatively by perfusing radiolabeled molecules of various sizes through the anterior chamber and examining the different pathways by which the tracers left the eye (Bill, 1962, 1965, 1966a, 1966c, 1966d). By

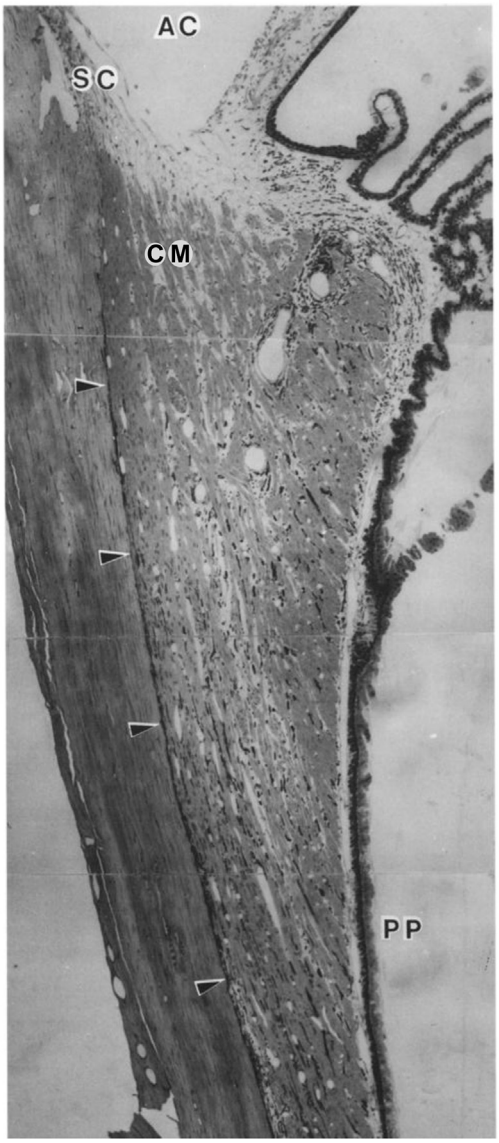

Fig. 1. Meridional section through the uveal tract of a *Macaca fascicularis*. Arrowheads show supraciliary and suprachoroidal space. Unconventional outflow passes from the anterior chamber (AC), through the most posterior aspects of the uveal meshwork, enters the open spaces between longitudinal aspects of the ciliary muscle (CM) and then enters the suprachoroidal space. SC – Schlemm's canal; PP – pars plana. Reprinted from (Wood et al., 1990) with permission from Springer.

Please cite this article in press as: Johnson, M., et al., Unconventional aqueous humor outflow: A review, Experimental Eye Research (2016), http://dx.doi.org/10.1016/j.exer.2016.01.017