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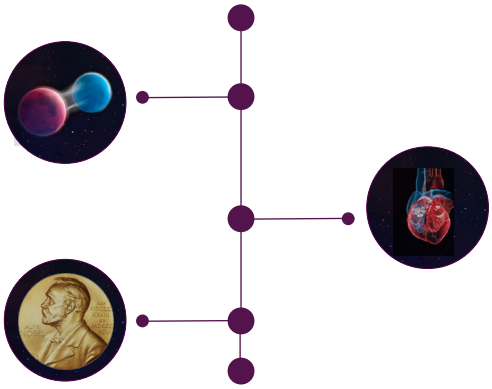
NITRIC OXIDE:
250 YEARS OF INNOVATION AND DISCOVERY

Nitrates were first recognized for their vasodilatory effect over 150 years ago. Since then, the understanding of nitric oxide as a physiological "relaxer" molecule has evolved dramatically, and it is now established as a key mediator of ocular health.[1-4]

EARLY VASCULAR INSIGHTS AND DISCOVERIES



1775

FIRST DISCOVERY OF NITRIC OXIDE

Nitric oxide is discovered by English chemist Joseph Priestley.[1]

1860s

NITRATES HARNESSED TO TREAT VASCULAR DISEASE

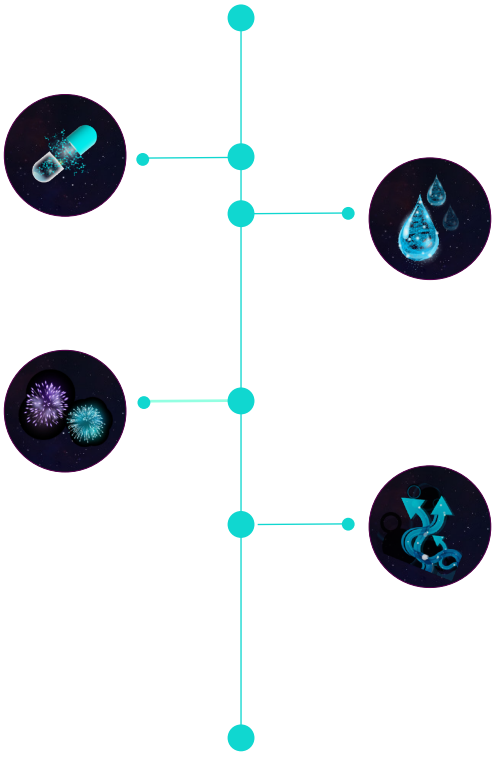
T. Lauder Brunton and William Murrell pioneer the use of nitrates for the treatment of angina and hypertension.[1]

1977–1987

NITRIC OXIDE ESTABLISHED AS A KEY CARDIOVASCULAR SIGNALING MOLECULE

Landmark research by Robert Furchgott, Louis Ignarro, and Ferid Murad establishes nitric oxide as the key effector of vascular smooth muscle cell relaxation, leading to the 1998 Nobel Prize in Physiology/Medicine.[1]

NITRIC OXIDE AND IOP



1980

SYSTEMIC NITRATES FOUND TO LOWER IOP

Angelika and Volker Wizemann report that a short course of oral organic nitrates leads to a drop in IOP.[4]

MARCH 1992

TOPICAL NITROGLYCERIN SHOWN TO EFFECTIVELY LOWER IOP

In a tonographic study of rabbit eyes, James Nathanson and colleagues are the first to suggest that topical nitrovasodilators may be effective ocular hypotensive agents for individuals with elevated IOP.[5]

DECEMBER 1992

NITRIC OXIDE NAMED "MOLECULE OF THE YEAR"

Science proclaims nitric oxide the molecule of the year based on widespread recognition of its multitude of critical physiological functions throughout the body.[6]

1994

EXOGENOUS NITRIC OXIDE RELAXES THE TRABECULAR MESHWORK

Exogenous nitric oxide is found to reduce outflow resistance within the trabecular meshwork (TM) and ciliary muscle of bovine eyes. The TM is postulated as a resistance system regulating outflow and modulated by "hormonal contractile and relaxing influences."[7]

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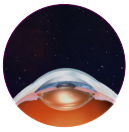
NITRIC OXIDE AND CONVENTIONAL OUTFLOW



1995

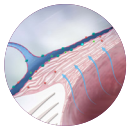
ANTERIOR EYE ENRICHED IN eNOS

Nathanson and colleagues discover that endothelial nitric oxide synthase (eNOS) is constitutively expressed throughout Schlemm's canal in the human conventional outflow pathway. Endogenous nitric oxide is hypothesized to play a key role in regulating outflow resistance.[8]

1998

eNOS GENE MUTATIONS ASSOCIATED WITH ELEVATED POAG RISK

Polymorphisms in the *NOS3* gene are associated with primary open-angle glaucoma (POAG). This is later confirmed in large, population-based case-control studies.[9,10]



2002/2004

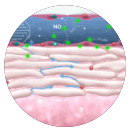
NITRIC OXIDE MARKERS DEPLETED IN GLAUCOMATOUS EYES

Two separate groups demonstrate that nitric oxide markers within aqueous humor are reduced by up to 40% in patients with glaucoma vs healthy controls.[11,12]

2011

eNOS OVEREXPRESSION LOWERS IOP

Utilizing an eNOS transgenic mouse model, Dan Stamer and colleagues demonstrate that eNOS overexpression within endothelial cells of the eye lowers IOP by increasing pressure-dependent outflow.[13]



2014

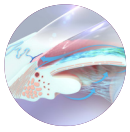
SHEAR STRESS-TRIGGERED NITRIC OXIDE RESTORES IOP HOMEOSTASIS

When IOP is elevated, shear stress within Schlemm's canal triggers nitric oxide production. This physiologic signaling cascade mirrors that observed in maintenance of vascular tone.[14]

2016

HIGH DIETARY NITRATE INTAKE ASSOCIATED WITH LOWER POAG RISK

Among 1,483 patients with POAG, those with higher dietary intake of nitrates, primarily sourced through green leafy vegetables, demonstrate reduced risk level of both POAG and POAG subtypes.[15]



2018

NITRIC OXIDE DILATES VESSELS OF THE DISTAL OUTFLOW TRACT

In separate studies using a porcine anterior segment perfusion model, Susannah Waxman and colleagues, as well as Fiona McDonnell and Dan Stamer, respectively, demonstrate that endogenous nitric oxide can dilate distal vessels of the conventional outflow tract in a TM-independent fashion, establishing distal vessels as an additional site of aqueous outflow resistance.[16,17]

Stay up to date on emerging research in nitric oxide and its role in ocular health and disease.

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