# NITRIC OXIDE/cGMP SIGNALING PATHWAY EXERTS TONIC CONTROL ON INTRAOCULAR PRESSURE (IOP) HOMEOSTASIS IN RABBITS

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The Nitric oxide (NO)/guanylate cyclase pathway plays a major role in aqueous humor dynamics and thus, it represents a potential drug target for the treatment of hypertensive glaucoma.
To investigate the involvement of NO/cGMP pathway on intraocular pressure (IOP) homeostasis, we evaluated basal IOP and basal aqueous humor cGMP levels (a marker of biologically active NO) respectively in spontaneously "high IOP" Dutch Belted (HP-DB) and "low IOP" New Zealand White (LP-NZW) normotensive rabbits. HP-DB rabbits had significantly higher basal IOP compared to LP-NZW rabbits (32.0±1.2 mmHg and 20.0±0.9 mmHg, respectively; $p<0.05$), along with significantly ($p<0.05$) lower basal cGMP levels (5.6±0.4 nM and 21.9±1.2 nM, respectively). To further exploit the time- and cause-relationship between NO/cGMP signaling and IOP we then assessed the kinetic profile of the IOP-lowering effects of topically administered SNAP (0.15%), a well known NO/cGMP signaling activator, and the respective cGMP levels in LP-NZW rabbit aqueous humor sampled at several time points following instillation. Albeit slightly, SNAP significantly reduced basal IOP with a maximal effect at 30 min ($\Delta\Delta_{max}$= 2.37±0.57 mmHg, 10 % reduction). The effects lasted up to 60 min after treatment and decayed thereafter. Conversely, cGMP levels in aqueous humor started to increase as soon as 15 min after the treatment, reaching maximal levels at 60 min and returned towards basal values at 180 min (153±10, 212±16, 306±49 and 182±10 % of basal at 15, 30, 60 and 180 min, respectively). Taken together these data suggest that NO/cGMP signaling pathway likely exerts tonic control on aqueous humor dynamics and, consequently on IOP. Furthermore, our data suggest that NO-donor drugs alone or combined with approved therapies (*i.e.* prostaglandin, β-blockers) might ultimately translates in an efficient IOP-lowering strategy in ocular dysfunctions associated with high IOP and impaired NO/cGMP signaling such as glaucoma.