AB029. The role of inducible nitric oxide synthase in deleterious effects of Kinin B1 receptor in diabetic retinopathy

Rahmeh Othman[1,2], Elvire Vaucher[1], Réjean Couture[2]

[1]Laboratoire de Neurobiologie de la Cognition Visuelle, École d'optométrie, [2]Département de pharmacologie et physiologie, Université de Montréal, Montréal, QC, Canada

Background: Overexpression of inducible nitric oxide synthase (iNOS) has been reported in diabetic retinopathy (DR). The kinin B1 receptor (B1R) is also overexpressed in DR, and can stimulate iNOS via Gαi/ERK/MAPK pathway. We previously showed that the topical administration of a B1R antagonist, LF22-0542, significantly reduces leukocyte infiltration, increased vascular permeability and overexpression of several inflammatory mediators, including iNOS in DR. Thus, the aim of this study was to determine whether the pro-inflammatory effects of B1R are attributed to oxidative stress caused by the activation of iNOS pathway in order to identify new therapeutic targets for the treatment of DR. iNOS and B1R being absent in the normal retina, their inhibition is unlikely to result in undesirable side effects. The approach will be no invasive by eye application of drops.
Methods: Diabetes was induced in male Wistar rats (200–230 g) by a single intraperitoneal injection of streptozotocin (STZ, 65 mg/kg b.w). One week later, rats were randomly divided into four groups (N=5) and treated for one week as follows: Gr 1: control rats treated with the selective iNOS inhibitor (1,400 W, 0.06 µM twice a day by eye-drops ×7 days), Gr 2, STZ-diabetic rats treated with 1,400 W, Gr 3: control rats received a selective B1R agonist [Sar (D-Phe8)-des-Arg9-BK, 100 µg twice a week] by intravitreal injections (itrv) and treated with 1,400 W, Gr 4: STZ-diabetic rats + B1R agonist +1,400 W. At the end of treatment and two weeks post-STZ, three series of experiments were carried out to measure vascular permeability (by Evans blue dye method) and the expression of vasoactive and inflammatory mediators, including iNOS, VEGF-A, VEGF-R2, IL-1β, Cox-2, TNF-α, bradykinin 1 and 2 receptors and carboxypeptidase M/kininase 1 (by Western Blotting and qRT-PCR). The nitrosative stress (nitrosylation of proteins) was also assessed by Western Blotting. One-way Anova test with Bonferroni post hoc was used for statistical analysis.
Results: STZ-diabetic rats showed a significant increase in retinal vascular permeability (22.8 µg/g Evans blue dye per g of fresh retinas, P=0.016) compared with control rats and control treated rats (17.2 and 16.8 µg/g respectively). The injections of B1R agonist amplified the increase of vascular permeability which was normalized by the 1,400 W. The overexpression of inflammatory markers was also normalized by the 1,400 W in STZ-diabetic rats received or not the B1R agonist.
Conclusions: These results support a contribution of iNOS in the deleterious effects of B1R in this model of diabetic retinopathy. Hence, iNOS inhibition by ocular application of 1,400 W may represent a promising and non-invasive therapeutic approach in the treatment of diabetic retinopathy.
Keywords: Rétinopathie diabétique; inducible nitric oxide synthase (iNOS); B1 receptor (B1R)

doi: 10.21037/aes.2018.AB029
Cite this abstract as: Othman R, Vaucher E, Couture R. The role of inducible nitric oxide synthase in deleterious effects of Kinin B1 receptor in diabetic retinopathy. Ann Eye Sci 2018;3:AB029.

