Insulin growth factor works synergistically with dopamine to attenuate diabetic retinopathy by downregulating vascular endothelial growth factor.

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Abstract: Background: Diabetic retinopathy (DR) involves neurodegeneration accompanied with vascular damage leading to vision loss. Angiogenesis characterizes the disease progression from the Non Proliferative Diabetic Retinopathy (NPDR) into the advanced stage known as Proliferative Diabetic Retinopathty (PDR). Dopamine (DA) deficiency in addition to low levels of insulin like growth factor (IGF-1) marks the NPDR stage and increasing IGF-1 manifests into PDR. Although IGF-1 proved to be proangiogenic manifesting neovascularization in the PDR stage but regulation of IGF-1 levels with adequate DA may delay the onset of angiogenesis.

Materials and Method :A group of 40 Wistar rats were maintained for a period of 8, 12 and 16 weeks after induction of diabetes with streptozotocin (STZ) and subsequently treated with DA and DA with IGF-1 in combination. The cytotoxicity of the combination is tested in retinal pigment epithelium(ARPE-19) cell line . The retinae from treated animals were assessed for morphological changes through H & E staining and TEM, DA level analyzed by HPLC, antiangiogenic mechanism of action confirmed through tube formation assay in HUVEC cell line and protein expression patterns of Akt, pAkt, Erk and pErk , recceptor levels by RT-PCR and immunofluorescence.

Results :Improved retinal morphology were observed in response to 10mg/kg body weight of rats , DA as well as combination of DA and 2µl /eye of IGF-1. DA levels were significantly low in 16 weeks as compared to 12 weeks in retina and these levels were supported by DA levels in serum. The levels of angiogenic markers VEGFR1 and VEGFR2 were enhanced in 16 weeks compared to 12 weeks which was supported by tube formation assay in HUVEC cells .Consequently Dopamine receptors DR1, DR2,DR4 and insulin growth factor -1 receptor, IGF-1R were also decreased in these time points which could be augmented by administration of DA in combination with IGF-1.Increased expression of pAkt and pErk indicates involvement of phosphoinositol pathway. The synergistic antiangiogenic effect of DA and IGF-1 was also established in an alternate CAM model Inhibition of angiogenic factors causing vascular proliferation needs to be well timed in order to prevent the progression of NPDR to PDR stage.

Conclusion : L-DOPA at concentrations of 10mg/kg body was able to attenuate IGF-1 induced hypervascularization as visible through H & E staining and TEM. This is the first reported study to highlight the downregulation of vascular endothelial growth factor(VEGF) levels through dopamine induced regulation of insulin growth factor (IGF-1). The symptoms of PDR like onset of neovascularization due to disruptions in dopaminergic neurons and increased IGF-1 levels could be prevented by combination of DA and IGF-1.