**“Angiogenesis and VEGF-A pathway are involved in the mechanism by which INGAP_PP increases B-cell mass and function.”**

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Background:
Islet angiogenesis is needed for embryonic β-cell differentiation and INGAP-PP administration increases Beta-cell mass and function in rats.
Aim:
To determine the role of islet angiogenesis in the mechanism by which INGAP-PP enhances β-cell mass and function.
Methods:
*In vivo*: adult Wistar rats were treated (ip) for 10 days with saline (Control) or INGAP-PP (500μg/day). Thereafter, serum parameters levels were measured and HOMA-IR and – β were calculated. Cell apoptotic rate and gene expression (qPCR and western blot) of angiogenesis and apoptotic markers were determined. *In vitro*: islets isolated from normal rats were cultured for 4 days in different composition: Control; INGAP-PP (10μg/ml); Rapamycin (10ng/ml + control or INGAP-PP); and VEGF (10ng/ml). We determined VEGF released to the medium (ELISA) and glucose-stimulated insulin secretion (RIA) Statistics: ANOVA and t test; significant differences were considered when $p<0.05$ (*).
Results:
*In vivo*: INGAP-PP administration did not affect serum parameters and HOMA indexes, but significantly decreased apoptotic rate ($p<0.05$). It also increased mRNA levels of integrin, VEGF, VEGFR, laminin and Bcl-2 and decreased Bad, caspase-8, -9 and -3. It also increased protein concentration of integrin, VEGF and Bcl-2 while decreased Bad, caspase-8, -9 and -3. *In vitro*: INGAP-PP increased significantly VEGF release into culture medium. Insulin secretion in INGAP-PP and VEGF, significantly increased in response to 16.6mM glucose. Rapamycin significantly decreased the enhancing effect of INGAP-PP.
Conclusion:
The enhancing effect of INGAP-PP, either *in vivo* or *in vitro*, on glucose-induced insulin secretion was significantly associated with an increase of vascular neogenesis markers and a reduction of pro-apoptotic gene expression. The data suggest the active involvement of angiogenesis and VEGF pathway in the mechanism by which INGAP-PP increases β-cell mass and function.