



Università degli Studi di Catania
Dipartimento di Scienze bio-mediche



Retinal protection: role of PACAP and NAP

Soraya Scuderi

IT-ARVO Chapter meeting – Catania, 3-4 Febbraio 2014



Il diabete mellito

- ✓ **Diabete mellito: l'epidemia del XXI secolo**
- ✓ **439 milioni diabetici nel 2030**
- ✓ **Un nuovo diabetico ogni 9,9 secondi**

La retinopatia diabetica: i fatti

- ✓ **Prevalenza nella popolazione diabetica: 33,2%**
- ✓ **Prevalenza delle forme che compromettono
la capacità visiva: 7,9%**

La retinopatia diabetica: il trattamento

“from bench to bedside”

- ✓ Prevenire/trattare l'iperpermeabilità
- ✓ Ridurre/eliminare l'ipossia tissutale
- ✓ Considerare la neuroprotezione

Neuropeptide (abbreviation)	Neuronal	Müller cell	Pigment epithellum	Extrinslc, having receptors	Receptors
Angiotensin II (AT) [20–22]	U	+	+	++	AT1R and AT2R
Bradykinin (BK) [50, 51]		?	+	+	B1R
Cortistatin (Cst) [23]	U	—	++	—	SST 1, 2 and 4 receptors
Enkephalins (Enk) [27]	A	—	—	—	sigma
Erythropoietin (EPO) [52, 53]	?	+		++	EPO-R
Neurokinin A and B (NKA and NKB) [54]	A, G	—	—	—	NK-1R and NK-3R
Neuropeptide Y (NPY) [25–27]	A, G	—	—	—	Y1, Y2, Y4 and Y5
Neurotensin/LANT6 (NT) [55]	A, G	—	—	—	Not known
Orexin A and B (OXA and OXB) [56]	A, G	—	+	+	OX-R1
Pituitary adenylate cyclase-activating peptide (PACAP) [32]	A, G	—	—	—	PAC-1R; VPAC1 and 2
Secretoneurin (SN) [57]	A, G	—	—	—	Not known
Somatostatin (Sst) [26, 36, 37, 39]	A, dA	—	—	—	SST1, 2 and 4 receptors
Substance P (SP) [27, 43, 47]	A, G	—	—	—	NK1R and NK3R
Thyrotrophin-releasing hormone (TRH) [58]	A	—	—	—	TRH-R1 and -R2
Urocortin (UCN) I, II and III [24, 59]	?	—	+	—	CRF-1R
Vasoactive intestinal polypeptide (VIP) [26, 46, 47]	A, dA	—	—	—	VPAC1 & 2

Abbreviations are as follows: A, amacrine cell; dA, displaced amacrine cell; G, ganglion cell; U, unidentified cell type; +, present; ++, present in high quantity; and ?, not certified.

PACAP (*Pituitary Adenylate Cyclase-Activating Polypeptide*)

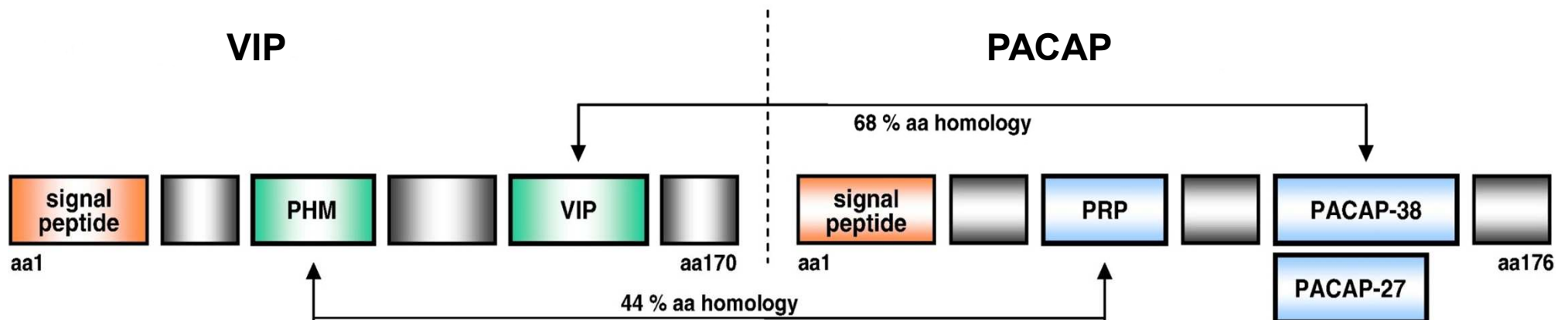
Le forme biologicamente attive sono:

PACAP38 (38 aminoacidi)

PACAP27 (27 aminoacidi)

VIP (*Vasoactive Intestinal Polypeptide*)

Unica forma biologicamente attiva di 28 aminoacidi



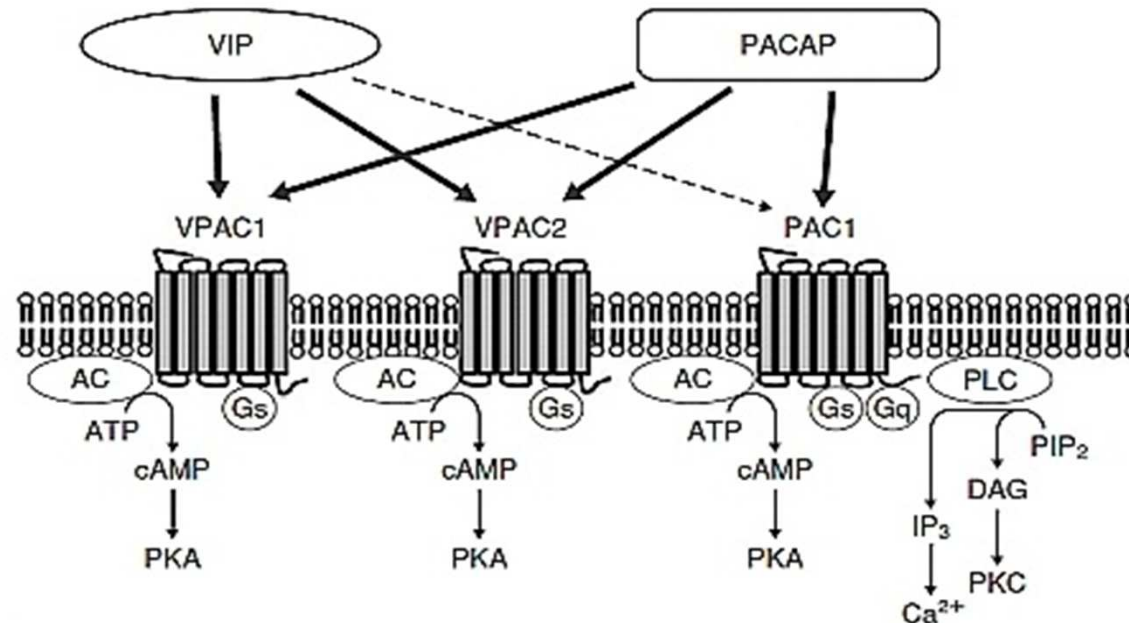
PACAP e VIP si legano a specifici recettori di membrana

PAC1

VPAC

VPAC1

VPAC2





Contents lists available at SciVerse ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides



Early changes in pituitary adenylate cyclase-activating peptide, vasoactive intestinal peptide and related receptors expression in retina of streptozotocin-induced diabetic rats

Salvatore Giunta^a, Alessandro Castorina^a, Claudio Bucolo^b, Gaetano Magro^c, Filippo Drago^b,
Velia D'Agata^{a,*}

Livelli di espressione mRNA del peptide PACAP, VIP e dei loro recettori PAC1/VPAC

	1 settimana		3 settimane	
	Veicolo Fold change \pm sem	Streptozotocina Fold change \pm sem	Veicolo Fold change \pm sem	Streptozotocina Fold change \pm sem
PACAP	1.06 \pm 0.25	4.24 \pm 0.33**	1.00 \pm 0.05	0.76 \pm 0.02*
VIP	1.01 \pm 0.09	5.71 \pm 0.24***	1.00 \pm 0.06	0.74 \pm 0.01*
PAC1	1.03 \pm 0.17	0.6 \pm 0.01	1.00 \pm 0.02	0.45 \pm 0.03***
VPAC1	1.03 \pm 0.17	2.83 \pm 0.28**	1.00 \pm 0.02	0.79 \pm 0.02**
VPAC2	1.02 \pm 0.14	3.55 \pm 0.43**	1.00 \pm 0.03	0.76 \pm 0.02**

*p<0.05, **p<0.01 or ***p<0.001 vs vehicle , two-tailed Student *t*-test.

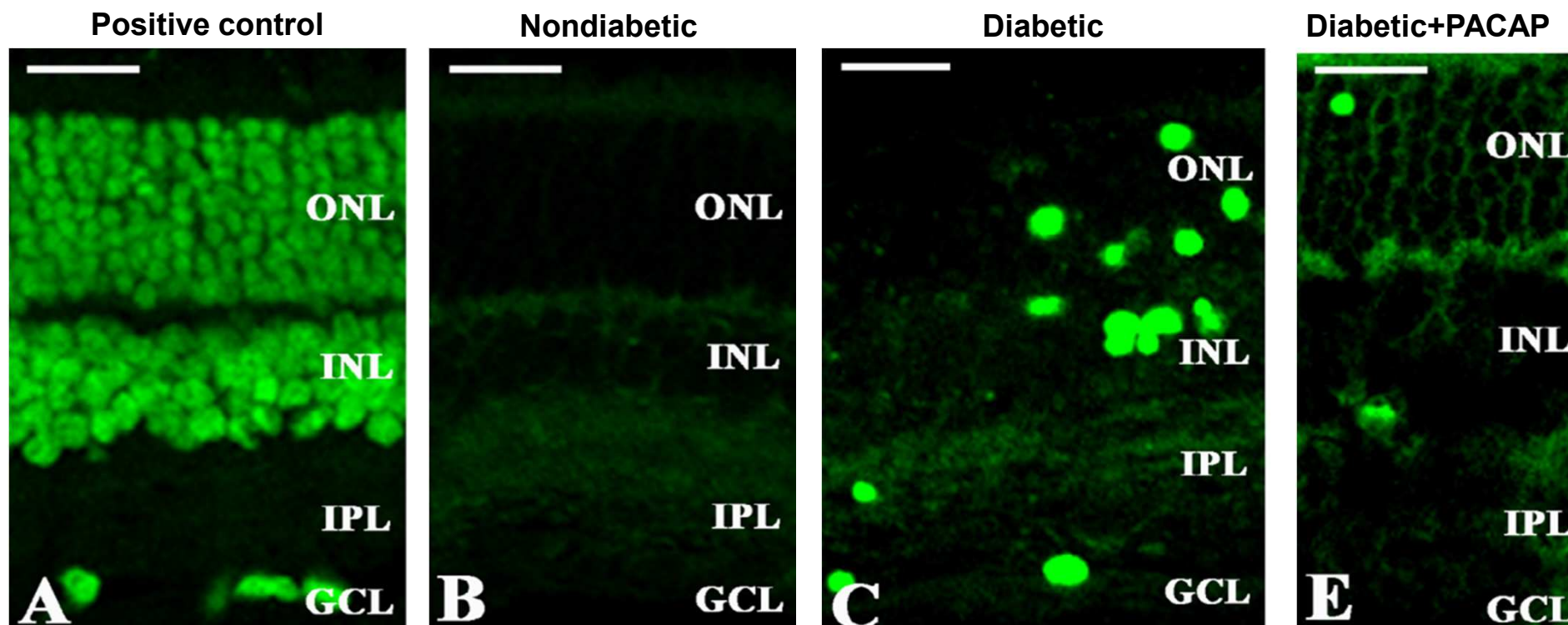
Livelli di espressione dei geni bcl-2 e p53 nella retina dei ratti dopo somministrazione di PACAP38 per via endoculare

Trattamento	Bcl-2 Fold change \pm sem	p53 Fold change \pm sem
veicolo ip + veicolo iv	1.00 \pm 0.08	1.00 \pm 0.06
veicolo ip + PACAP iv	1.10 \pm 0.03	0.94 \pm 0.02
streptozotocina ip + veicolo iv	0.77 \pm 0.02*	1.65 \pm 0.06**
streptozotocina ip + PACAP iv	1.10 \pm 0.08[#]	0.51 \pm 0.01[#]

*p<0.05 vs veicolo + veicolo; **p<0.001 vs veicolo + veicolo; #p<0.001 vs streptozotocina + veicolo
two-tailed Student *t*-test.

Antiapoptotic effects of PACAP

Tunel assay





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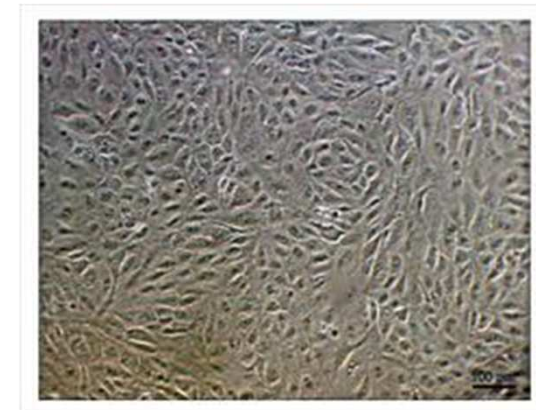
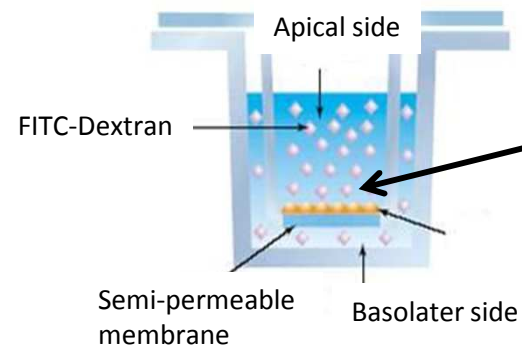


Ameliorative effect of PACAP and VIP against increased permeability in a model of outer blood retinal barrier dysfunction

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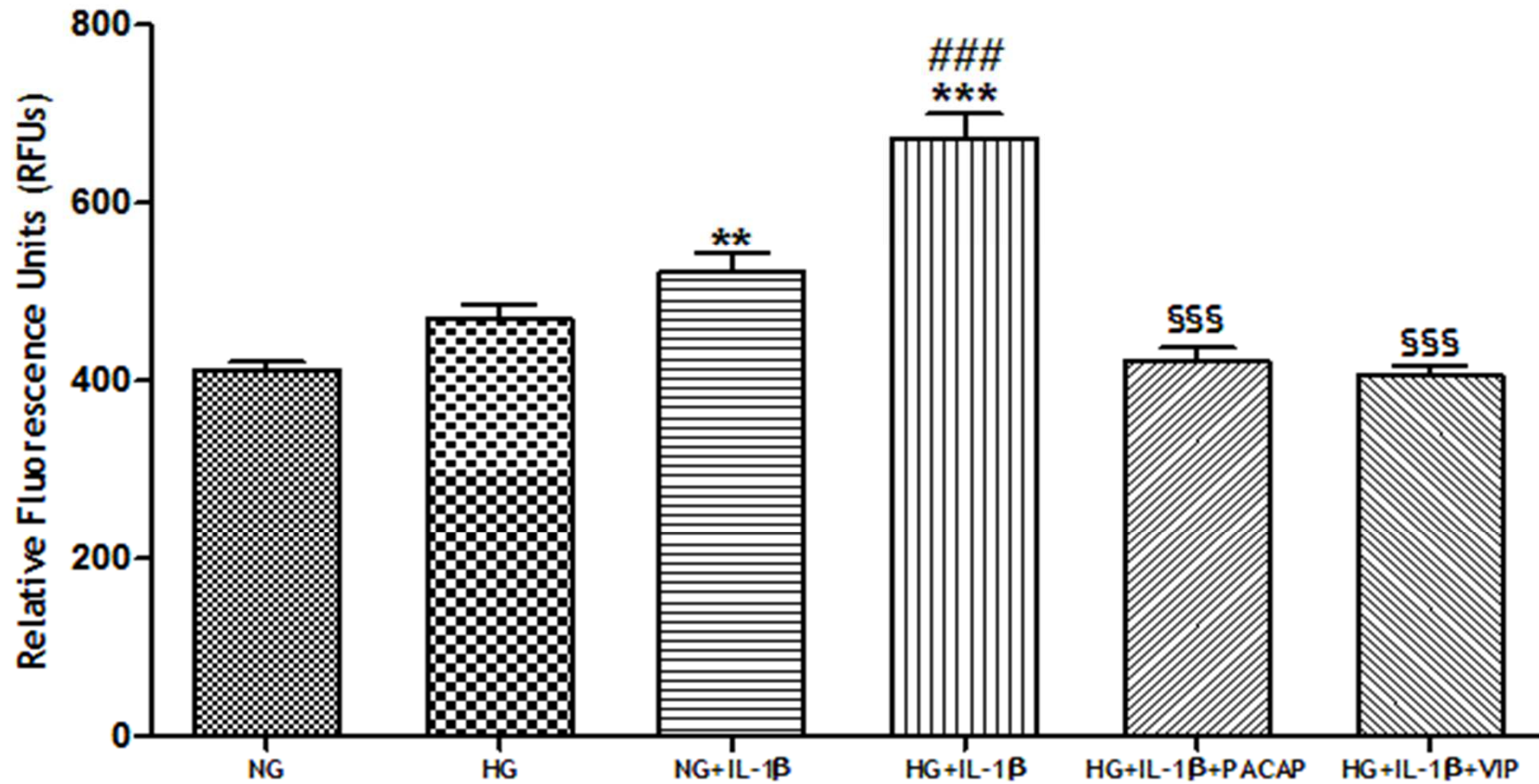
^a Department of Bio-Medical Sciences, University of Catania, Catania, Italy

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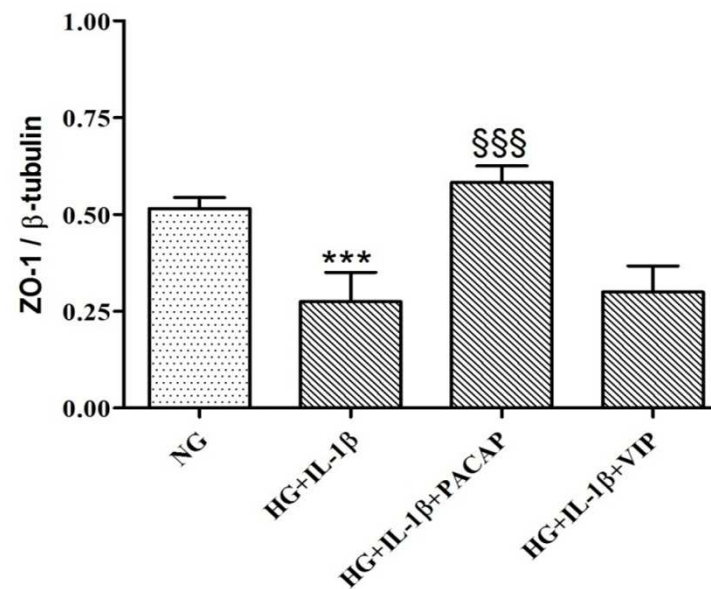
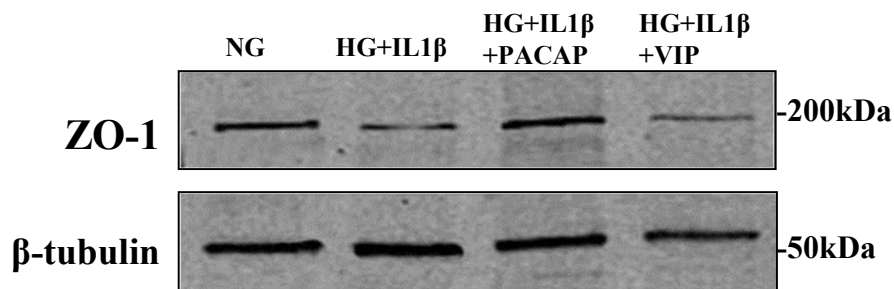
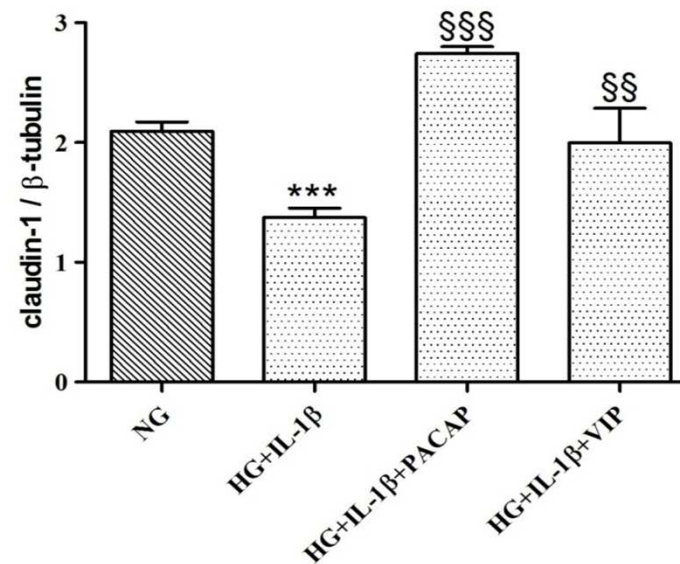
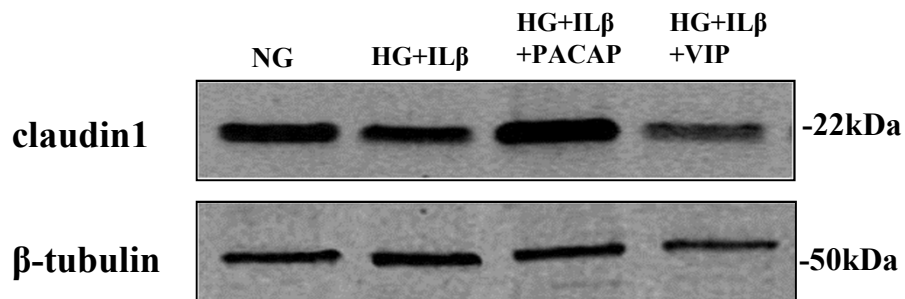


Arpe 19 cells

Analisi della permeabilità con destrano coniugato con FITC



p<0,01 vs NG; *p<0,001 vs NG; ###p<0,001vs HG; §§§p<0,001 HG+IL-1 β
One Way ANOVA, Post hoc test Tukey



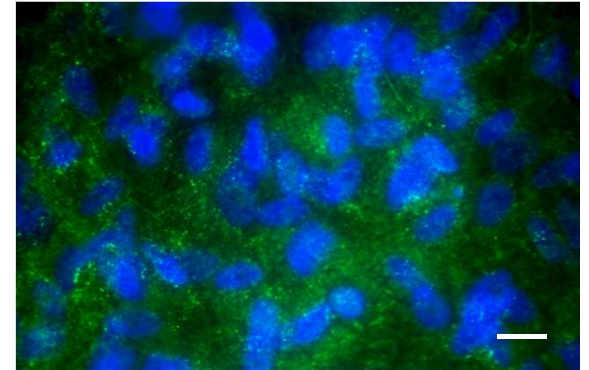
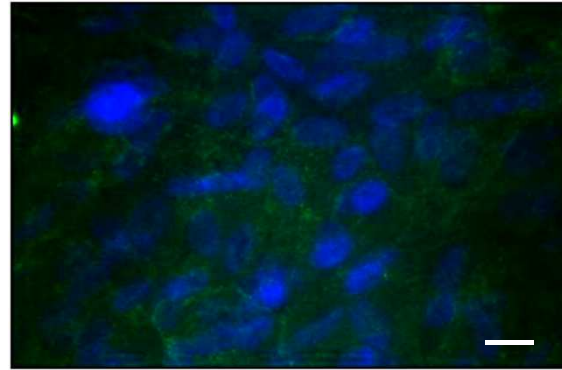
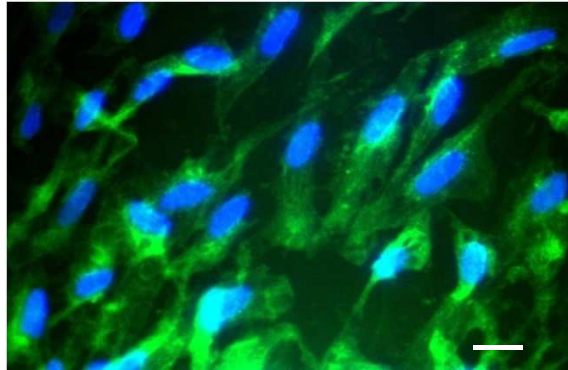
*** p <0.001 vs NG, §§ p <0.01 vs HG+IL-1 β , §§§ p <0.001 vs HG+IL-1 β One Way ANOVA

NG

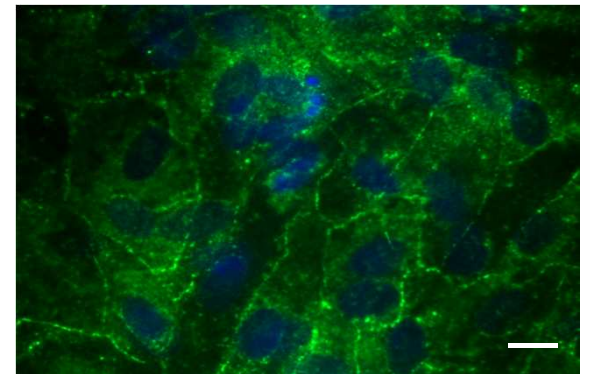
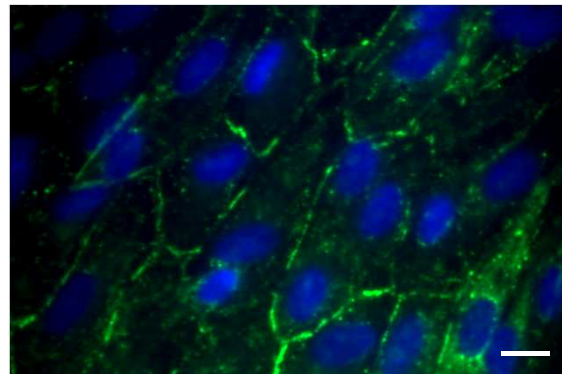
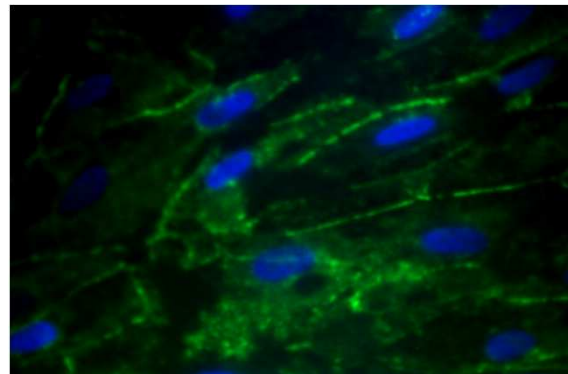
HG+IL-1 β

HG+IL-1 β +PACAP

claudin



ZO-1



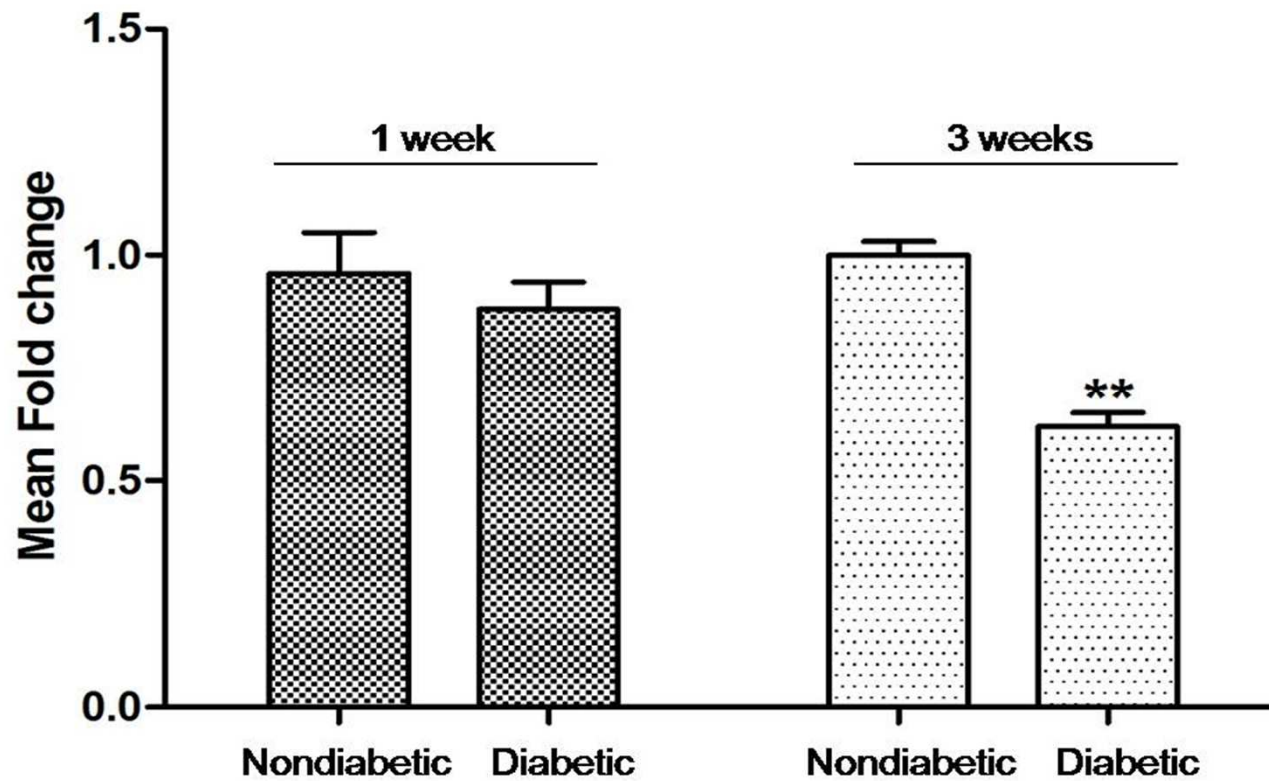
Davunetide (NAP) Protects the Retina Against Early Diabetic Injury by Reducing Apoptotic Death

**Soraya Scuderi • Agata Grazia D'Amico • Alessandro Castorina • Concetta Federico •
Giuseppina Marrazzo • Filippo Drago • Claudio Bucolo • Velia D'Agata**

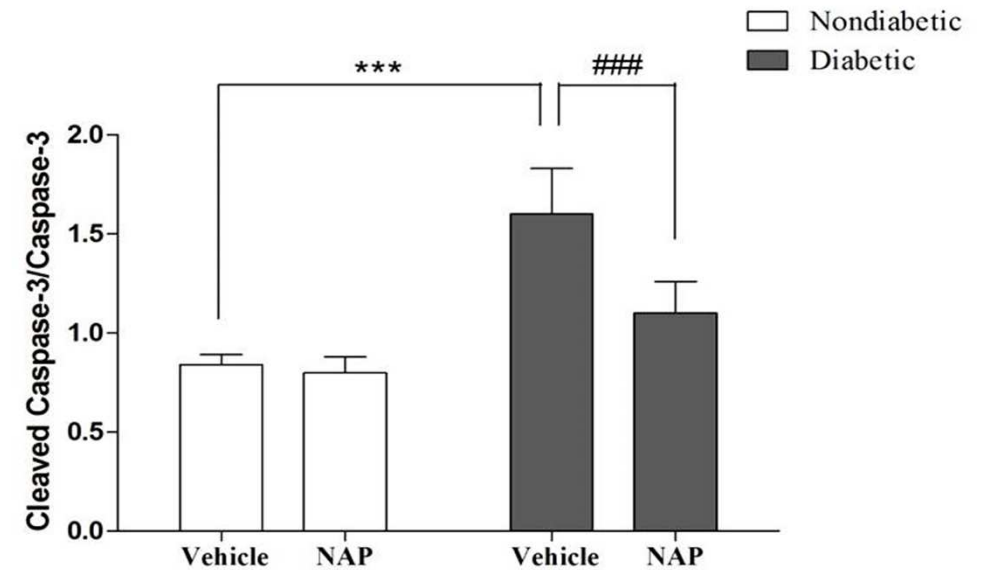
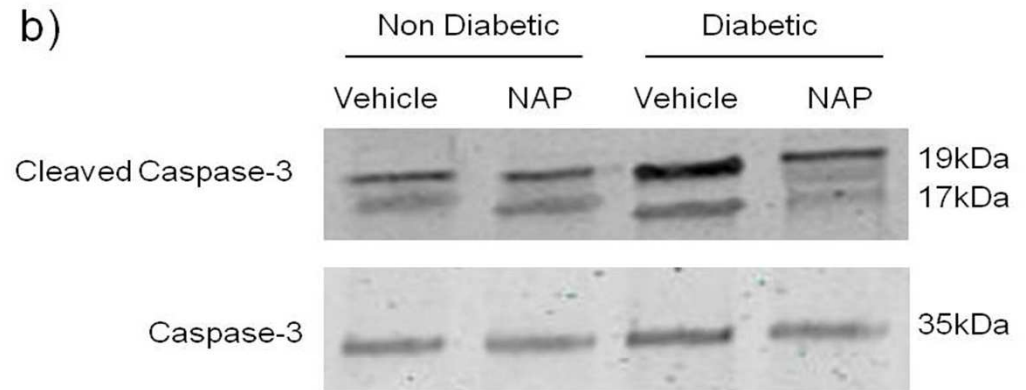
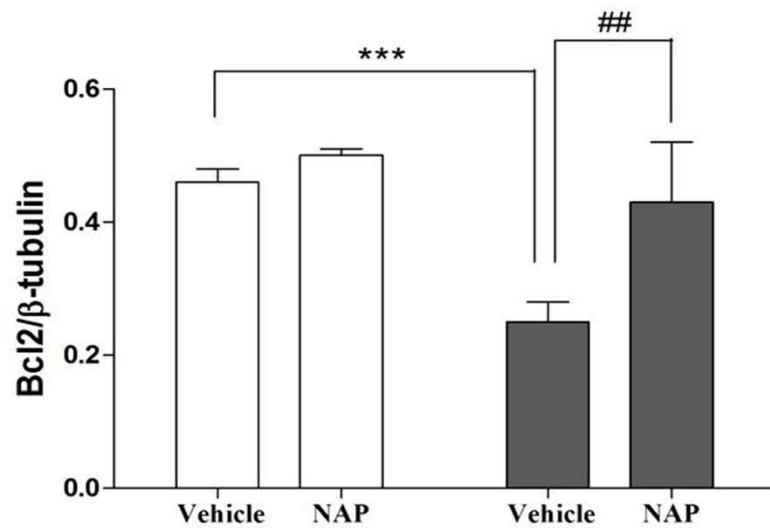
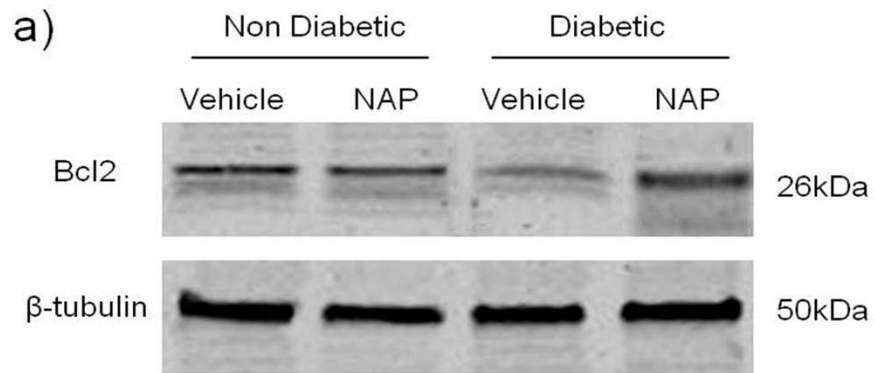
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OF

Livelli di espressione del mRNA dell'activity-dependent neurotrophic protein (ADNP)



**p<0.01 vs nondiabetic+ vehicle



*** $p < 0.001$ vs nondiabetic+ vehicle; ## $p < 0.01$ or ### $p < 0.001$ vs diabetic+veichle

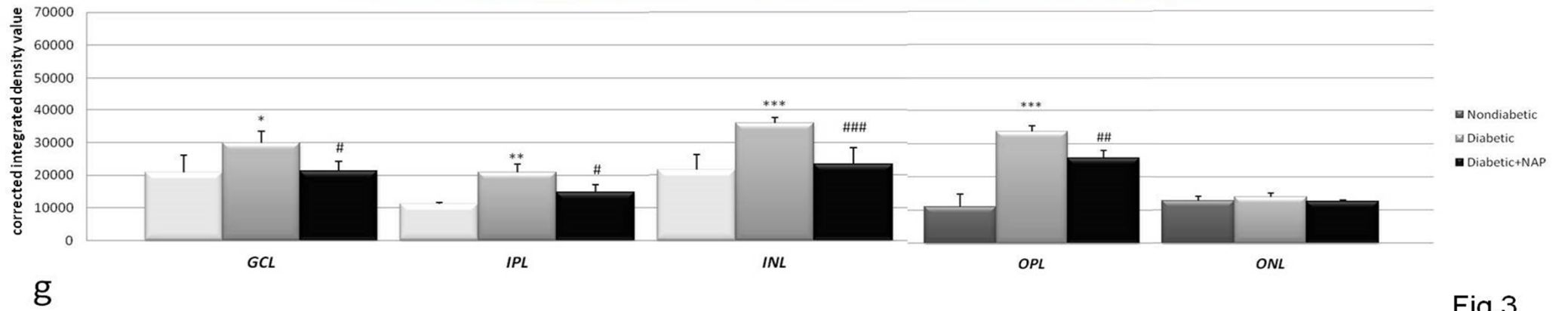
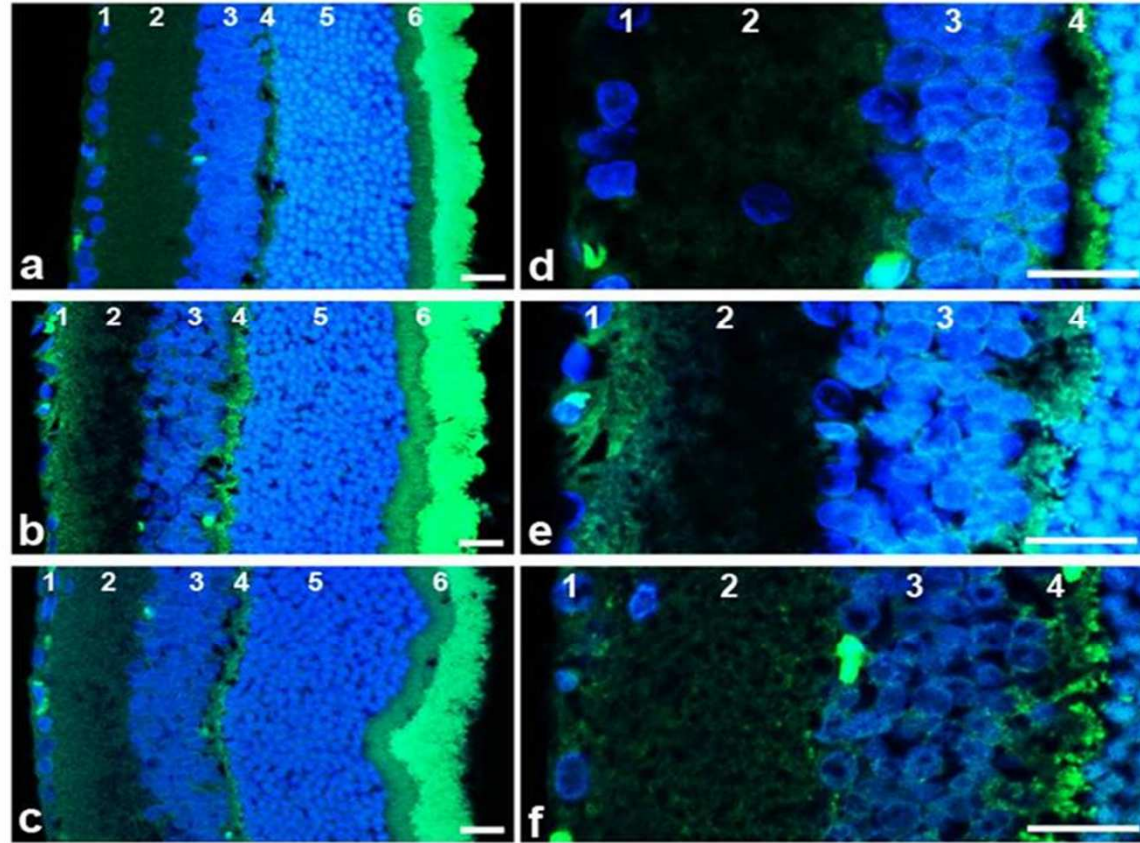


Fig.3

Conclusioni

- Il PACAP38 ed il NAP hanno un effetto protettivo dal danno retinico indotto dall'iperglicemia
- L'effetto del PACAP38 potrebbe essere mediato anche attraverso l'aumento intracellulare del peptide ADNP
- L'azione protettiva del PACAP38 nella retinopatia diabetica potrebbe essere mediata dal mantenimento della funzionalità della barriera emato-retinica esterna



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Thank you for your attention!

