Muster-publikation Medizin

www.acad-write.com/leistungen/veroeffentlichung/

www.acad-write.com/aerzte/

www.acad-write.com/fachbereiche/medizin/

www.acad-write.com/leistungen/medical-writing/

Dr. Thomas Nemet

Modulation of immunity and autoimmunity by vasoactive intestinal peptide (VIP)

Introduction

Vasoactive intestinal peptide (VIP) is a neuropeptide with an pleiotropic action profile that includes systemic dilatory action on blood vessels, which can induce hypotension, increased cardiac output, respiratory stimulation, hyperglycemia, stimulation of intestinal secretion, and, rather surprisingly, immunomodulation (Said and Mutt, 1970; Barbezat and Grossman, 1971; Gonzalez-Rey, Anderson and Delgado, 2007). It was first isolated from the intestinal mucosa of the pig by Said and Mutt in 1970 (Said and Mutt, 1970). VIP is 18 amino acids in length and shorter c-terminal fragments show partial function (Bodanszky, Klausner and Said, 1973). Together with the structurally related incretin peptides Gastric inhibitory polypeptide (GIP) and Glucagon-like peptide-1 (GLP-1), it belongs to the secretin family (Bodanszky, Klausner and Said, 1973; Mutt, 1988).

The realization that certain patients with a rare form of pancreatic cancer who suffer from chronic diarrhea, flushing, and hypotension (pancreatic cholera syndrome or Verner–Morrison syndrome (Verner and Morrison, 1958)) have extremely elevated VIP levels in the blood stream, led to the discovery that VIP can induce adenylate cyclase activity (Schwartz *et al.*, 1974). Nowadays, it is known that VIP can bind to two receptors VPAC1 and VPAC2, both of which can also bind the related peptide Pituitary-Adenylate Cyclase Activating Peptide (PACAP) with similar affinity. PACAP can bind to another receptor PAC1, to which it has an approximately 100-fold higher affinity than VIP (Laburthe and Couvineau, 2002; Laburthe, Couvineau and Marie, 2002; Dickson and Finlayson, 2009). VPAC1, VPAC2, and PAC1 belong to the seven-transmembrane G-coupled receptor protein family and are differentially distributed throughout the body. While VPAC2 can be found in the skeletal and heart muscles, kidney, testis, stomach, pancreas, CNS, and adipose tissue, VPAC1 is restricted to the lung, liver, intestine, and CNS and is the predominant VIP binding receptor found on cells involved in the immune system, namely T-lymphocytes (McCulloch *et al.*, 2000; Groneberg *et al.*, 2001; Laburthe, Couvineau and Marie, 2002). Activation of VPAC1 or VAPAC2 results in activation of the adenylate cyclase and thus an increase in cellular cAMP levels (Couvineau and Laburthe, 2012).

VIP as an immunomodulatory molecule

As early as in the 1980ies, several research groups realized that binding of VIP to its cognate receptor on T-cells (VPAC1) can inhibit T-cell proliferation (Ottaway and Greenberg, 1984; Ottaway, 1987; Söder and Hellström, 1987). In respect to inhibition of T-cell proliferation, VIP acts synergistically with other intestinal neuropeptides like somatostatin and cholecystokinin (Tang, Braunsteiner and Wiedermann, 1992). While the specific actions and mechanisms of action of VIP were rather obscure during this period, it became clear early on that the role of VIP is not limited to being simply an inhibitor of T-cell proliferation and, thus, an immune suppressor. Rather, the interaction of VIP with its target cells is complex and depends on the surrounding environment, as it has differential and, in part, contradictory effects on specific cell populations, so that some of its effects on the immune system are indirect due to its effects on surrounding tissues like smooth muscle cells, secretory cells and the endothelium. Additionally, it can potentiate or inhibit the action of other signaling molecules (for review, see Bellinger *et al.*, 1996). It has, therefore, become customary to refer to VIP as an immunomodulatory rather than an immunosuppressive molecule.

One of the mechanisms of immunomodulation is that VIP can inhibit the production of proinflammatory cytokines like Interleukin (IL)-2, IL-4. IL-10, and IL-12; either by inhibiting their expression directly or indirectly by inhibiting cytokines like IL-2 that act as T-cell growth factors (Tang *et al.*, 1996; Wang *et al.*, 1996; Delgado, Munoz-Elias, *et al.*, 1999). However, the inhibition of cytokines by VIP is tissue-dependent and dependent on the presence or absence of other signaling molecules, which means it can have the opposite effect on cytokine expression depending on the environment. It has, for example, been shown to be able to synergize with the pro-inflammatory cytokine Tumor-necrosis factor (TNF) alpha in inducing the expression of IL-12 in human dendritic cells and induce their maturation (Delneste *et al.*, 1999). VIP is capable of directing an developing adaptive T-cell response toward a T-helper cell (TH) 2 cytokine profile by activating IL-4 and IL-5 productions, while simultaneously inhibiting typical TH1 cytokines like Interferon-gamma (IFNg) and IL-2 both *in vitro* and *in vivo* (Delgado, Leceta, *et al.*, 1999). This skewing of the T-cell response towards a TH2 response happens in large parts through the VIP-induced upregulation of expression of the costimulatory molecule CD86 (Delgado, Leceta, *et al.*, 1999; Delgado *et al.*, 2000). Chorny and co-workers were able to show that VIP was able to induce CD4+ CD25+ regulatory T-cells (Treg) in TCR-transgenic mice, when co-administered with the specific peptide (Chorny *et al.*, 2006). A possible mechanism for this in-vivo induction of Tregs is via the VIP-dependent

induction of tolerogenic dendritic cells (DC). Human monocytes that are cultured under DC-differentiating conditions in the presence of VIP develop a DC phenotype that is not fully mature and produces large amounts of IL-10. Co-culture of these tolerogenic DC with naïve CD4+ T-cells leads to the induction of T-cells with a regulatory T-cell 1 (TR1) phenotype and cytokine profile. Co-culture of the tolerogenic DC with CD+ T-cells induces IL-10-producing CD8+ CD28- CTLA4+ T cells. These CD4+ and CD8+ T-cells are both capable of inhibiting an antigen-specific TH1 response (Chorny, Gonzalez-Rey and Delgado, 2006; Gonzalez-Rey, Chorny, *et al.*, 2006).

There might be other mechanisms by which VIP can downregulate an ongoing inflammatory response. In Trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice, an animal model of Crohn's disease in humans, it has been shown that toll-like receptors (TLR)2 and TLR4, which are constitutively expressed in intestinal tissues, are overexpressed in the inflamed colon tissues. VIP can bring TLR2 and TLR4 expression level in this model down; close to normal levels (Arranz *et al.*, 2006).

While many of VIPs actions like the induction of TH2-type T-cells in the context of an inflammatory TH1-response, the induction of tolerogenic dendritic cells and regulatory T-cells, and downregulation of TLRs can act immunosuppressive, VIP can also prolong an ongoing inflammatory T-cell response. It has been shown to downregulate FAS ligand (FASL) on T-cells and, therefore, make them less sensitive to FAS/FASL-induced apoptosis. T-cell apoptosis via FAS/FASL is an important pathway to end an ongoing inflammatory T-cell response (Delgado and Ganea, 2000, 2001). VIP has also been shown to increase the IL-1 induced expression of the pro-inflammatory cytokine IL-6 in osteoblast (Persson and Lerner, 2005). However, it should be noted that inflammatory signals are necessary in the context of bone growth and healing to create an osteogenic environment (Herman, Krönke and Schett, 2008). Nevertheless, many actions of VIP are immunosuppressive, which has important implications for the potential therapeutic use of VIP in autoimmunity and other diseases with aberrant and exaggerated inflammation.

IL-17-producing T-cells were discovered in 2006 as the third kind of CD4+ effector cells with a distinct cytokine profile that has a crucial role in the induction of autoimmune responses. These T-cells, accordingly, were named TH17 and can be induced in vivo and in vitro by a combination of IL-6 and transforming growth factor beta (TGFb). TGFb alone can induce the expression of the transcription factor FOXp3, which is a marker of Tregs. TH17 cells produce large amounts of IL-17, IL-21, and IL-6 (Bettelli *et al.*, 2006). Interestingly, a combination of

VIP and IL-6 can induce IL-17-producing T-cells from naïve CD4+ T-cells, however, unlike regular TH17 cells, these cells do not produce IL-6 or IL-21 (Yadav and Goetzl, 2008; Yadav, Rosenbaum and Goetzl, 2008). This unusual TH17 population seems to be non-pathogenic and maintained by the presence of VIP (Jimeno *et al.*, 2014).

VIP immunomodulation in autoimmune disease

As shown in the previous section, VIP is an immunomodulatory peptide that acts as a downregulator of inflammatory responses in most microenvironments and tissue types. As such, it has great therapeutic potential for the treatment of autoimmune diseases, such as rheumatoid arthritis (Foey *et al.*, 2003). There is ample evidence for the efficacy of VIP in autoimmune disease, both natural and experimental.

The first reports of the use of VIP for the therapy of autoimmune diseases are from the early 2000s. Delgado and coworkers were successful in reducing both severity and incidence of collagen-induced arthritis (CIA) in mice (Delgado et al., 2001). Later work, which was conducted ex vivo, indicated that VIP was able to induce apoptosis and decrease proliferation in synovial cells from rats with established CIA. It also downregulated the expression of various pro-inflammatory cytokines like IL-1, TNFα, RANTES, and IL-6. It most likely exerted these actions through downregulation of expression and activity of NF-kappa B (Yin *et al.*, 2005). Additionally, VIP is able to induce CD4+ CD25+ Tregs in this model of rheumatoid arthritis and increase the number of T-cells with a TH2-like cytokine profile (Chen *et al.*, 2008). In addition to inducing CD4+ CD25+ Tregs in CIA in rats, VIP has been shown to reduce the TH1 and TH17 responses and induce TH2 responses (Deng *et al.*, 2010).

Chorny and co-workers were able to reduce the progression of both CIA and experimental autoimmune encephalitis (EAE) in rodent models by adoptive transfer of VIP-induced tolerogenic DC (Chorny et al., 2005). VIP-treated rodents showed reduced inflammation in the central nervous system and, consequently, reduce EAE neuropathology. It also selectively blocked the reactivity of encephalitogenic T-cell and, here, like in other models of autoimmunity, downregulated a large number of inflammatory mediators. Unlike many other experimental treatments of EAE, which are only effective as pretreatment, VIP showed treatment efficacy even after the disease was fully established and prevented relapses of the disease (Gonzalez-Rey, Fernandez-Martin, *et al.*, 2006). It is also effective as a preventive treatment before the induction of EAE (Fernandez-Martin, Gonzalez-Rey, Chorny, Martin, *et al.*, 2006). It is possible that these in vivo effects are due to the ability of VIP to induce Tregs

in this multiple sclerosis model (Chorny *et al.*, 2006; Fernandez-Martin, Gonzalez-Rey, Chorny, Ganea, *et al.*, 2006). Nevertheless, the ambivalent actions of VIP that can also exert pro-inflammatory actions were highlighted in a publication by Abad and coworkers. This group tried to induce EAE in a normally EAE-sensitive mouse strain in which the VIP gene was knocked out. To their surprise, the VIP KO-mice were nearly 100% resistant to EAE induction. Mice that did develop EAE symptoms showed a delayed onset and mild clinical symptoms. Adoptive transfer experiments and flow cytometry showed that immunization with myelin oligodendrocyte protein of the VIP-KO mice induced a robust antigen-specific T-cell response, with the T-cell from KO mice being able to induce EAE in WT mice, while T-cells from WT-mice with EAE were not able to induce EAE in VIP-KO mice. Histologic examination indicated that the defect might have lied with T-cell trafficking, as parenchymal infiltration was significantly impaired (Abad *et al.*, 2010).

VIP administration was also shown to have therapeutic effects in TNBS-induced colitis (Arranz *et al.*, 2006). Adoptive transfer of VIP-induced tolerogenic DC decreased diarrhea and weight loss in the same animal model. Histologic examination showed reduced colitis and histopathology (Gonzalez-Rey and Delgado, 2006). It is possible that VIP's influence on cell trafficking to the site of inflammation plays an additional role in its beneficial effects on TNBS-induced colitis (Arranz *et al.*, 2008). Yet, similar to the findings in the EAE model with VIP-KO mice, unexpected results were found when investigating the effect of disruption VIP signaling in this mouse model. Yadav and coworkers worked with KO mice in which either the VPAC1 or the VPAC2 VIP receptor gene was knocked out. Not unexpectedly, VPAC2-KO mice developed a faster and more severe form of TNBS-induced colitis. However, clinical symptoms were milder than in WT mice when TNBS-induced colitis was induced in VPAC1-KO mice (Yadav, Huang and Goetzl, 2011).

…. To be continued

References

Abad, C., Tan, Y.-V., Lopez, R., Nobuta, H., Dong, H., Phan, P., Feng, J.-M., Campagnoni, A. T. and Waschek, J. A. (2010) "Vasoactive intestinal peptide loss leads to impaired CNS parenchymal T-cell infiltration and resistance to experimental autoimmune encephalomyelitis.," *Proceedings of the National Academy of Sciences of the United States of America*, 107(45), pp. 19555–60. doi: 10.1073/pnas.1007622107.

Arranz, A., Abad, C., Juarranz, Y., Leceta, J., Martinez, C. and Gomariz, R. P. (2008) "Vasoactive intestinal peptide as a healing mediator in Crohn's disease.," *Neuroimmunomodulation*, 15(1), pp. 46–53. doi: 10.1159/000135623.

Arranz, A., Abad, C., Juarranz, Y., Torroba, M., Rosignoli, F., Leceta, J., Gomariz, R. P. and Martínez, C. (2006) "Effect of VIP on TLR2 and TLR4 expression in lymph node immune cells during TNBS-induced colitis.," *Annals of the New York Academy of Sciences*, 1070, pp. 129–34. doi: 10.1196/annals.1317.001.

Barbezat, G. O. and Grossman, M. I. (1971) "Intestinal secretion: stimulation by peptides.," *Science (New York, N.Y.)*, 174(4007), pp. 422–4.

Bellinger, D. L., Lorton, D., Brouxhon, S., Felten, S. and Felten, D. L. (1996) "The significance of vasoactive intestinal polypeptide (VIP) in immunomodulation.," *Advances in neuroimmunology*, 6(1), pp. 5–27.

Bettelli, E., Carrier, Y., Gao, W., Korn, T., Strom, T. B., Oukka, M., Weiner, H. L. and Kuchroo, V. K. (2006) "Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells," *Nature*, 441(7090), pp. 235–238. doi: 10.1038/nature04753.

Bodanszky, M., Klausner, Y. S. and Said, S. I. (1973) "Biological activities of synthetic peptides corresponding to fragments of and to the entire sequence of the vasoactive intestinal peptide.," *Proceedings of the National Academy of Sciences of the United States of America*, 70(2), pp. 382–4.

Chen, G., Hao, J., Xi, Y., Wang, W., Wang, Z., Li, N. and Li, W. (2008) "The therapeutic effect of vasoactive intestinal peptide on experimental arthritis is associated with CD4+CD25+ T regulatory cells.," *Scandinavian journal of immunology*, 68(6), pp. 572–8. doi: 10.1111/j.1365-3083.2008.02178.x.

Chorny, A., Gonzalez-Rey, E. and Delgado, M. (2006) "Regulation of dendritic cell differentiation by vasoactive intestinal peptide: therapeutic applications on autoimmunity and transplantation.," *Annals of the New York Academy of Sciences*, 1088, pp. 187–94. doi: 10.1196/annals.1366.004.

Chorny, A., Gonzalez-Rey, E., Fernandez-Martin, A., Pozo, D., Ganea, D. and Delgado, M. (2005) "Vasoactive intestinal peptide induces regulatory dendritic cells with therapeutic effects on autoimmune disorders.," *Proceedings of the National Academy of Sciences of the United States of America*, 102(38), pp. 13562–7. doi: 10.1073/pnas.0504484102.

Chorny, A., Gonzalez-Rey, E., Ganea, D. and Delgado, M. (2006) "Vasoactive intestinal peptide generates CD4+CD25+ regulatory T cells in vivo: therapeutic applications in autoimmunity and transplantation.," *Annals of the New York Academy of Sciences*, 1070, pp. 190–5. doi: 10.1196/annals.1317.011.

Couvineau, A. and Laburthe, M. (2012) "VPAC receptors: structure, molecular pharmacology and interaction with accessory proteins," *British Journal of Pharmacology*, 166(1), pp. 42–50. doi: 10.1111/j.1476-5381.2011.01676.x.

Delgado, M., Abad, C., Martinez, C., Leceta, J. and Gomariz, R. P. (2001) "Vasoactive intestinal peptide prevents experimental arthritis by downregulating both autoimmune and inflammatory components of the disease.," *Nature Medicine*, 7(5), pp. 563–568. doi: 10.1038/87887.

Delgado, M. and Ganea, D. (2000) "Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit T cell-mediated cytotoxicity by inhibiting Fas ligand expression.," *Journal of immunology (Baltimore, Md. : 1950)*, 165(1), pp. 114–23.

Delgado, M. and Ganea, D. (2001) "Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit expression of Fas ligand in activated T lymphocytes by regulating c-Myc, NF-kappa B, NF-AT, and early growth factors 2/3.," *Journal of immunology (Baltimore, Md. : 1950)*, 166(2), pp. 1028–40.

Delgado, M., Leceta, J., Gomariz, R. P. and Ganea, D. (1999) "Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide stimulate the induction of Th2 responses by up-regulating B7.2 expression.," *Journal of immunology (Baltimore, Md. : 1950)*, 163(7), pp. 3629–35.

Delgado, M., Leceta, J., Sun, W., Gomariz, R. P. and Ganea, D. (2000) "VIP and PACAP induce shift to a Th2 response by upregulating B7.2 expression.," *Annals of the New York Academy of Sciences*, 921, pp. 68–78.

Delgado, M., Munoz-Elias, E. J., Gomariz, R. P. and Ganea, D. (1999) "VIP and PACAP inhibit IL-12 production in LPS-stimulated macrophages. Subsequent effect on IFNgamma synthesis by T cells.," *Journal of neuroimmunology*, 96(2), pp. 167–81.

Delneste, Y., Herbault, N., Galea, B., Magistrelli, G., Bazin, I., Bonnefoy, J. Y. and Jeannin, P. (1999) "Vasoactive intestinal peptide synergizes with TNF-alpha in inducing human dendritic cell maturation.," *Journal of immunology (Baltimore, Md. : 1950)*, 163(6), pp. 3071–5.

Deng, S., Xi, Y., Wang, H., Hao, J., Niu, X., Li, W., Tao, Y. and Chen, G. (2010) "Regulatory effect of vasoactive intestinal peptide on the balance of Treg and Th17 in collagen-induced arthritis.," *Cellular immunology*, 265(2), pp. 105–10. doi: 10.1016/j.cellimm.2010.07.010.

Dickson, L. and Finlayson, K. (2009) "VPAC and PAC receptors: From ligands to function," *Pharmacology & Therapeutics*, 121(3), pp. 294–316. doi: 10.1016/j.pharmthera.2008.11.006.

Fernandez-Martin, A., Gonzalez-Rey, E., Chorny, A., Ganea, D. and Delgado, M. (2006) "Vasoactive intestinal peptide induces regulatory T cells during experimental autoimmune encephalomyelitis.," *European journal of immunology*, 36(2), pp. 318–26. doi: 10.1002/eji.200535430.

Fernandez-Martin, A., Gonzalez-Rey, E., Chorny, A., Martin, J., Pozo, D., Ganea, D. and Delgado, M. (2006) "VIP prevents experimental multiple sclerosis by downregulating both inflammatory and autoimmune components of the disease.," *Annals of the New York Academy of Sciences*, 1070, pp. 276–81. doi: 10.1196/annals.1317.026.

Foey, A. D., Field, S., Ahmed, S., Jain, A., Feldmann, M., Brennan, F. M. and Williams, R. (2003) "Impact of VIP and cAMP on the regulation of TNF-alpha and IL-10 production: implications for rheumatoid arthritis.," *Arthritis research & therapy*, 5(6), pp. R317-28. doi: 10.1186/ar999.

Gonzalez-Rey, E., Anderson, P. and Delgado, M. (2007) "Emerging roles of vasoactive intestinal peptide: a new approach for autoimmune therapy.," *Annals of the rheumatic diseases*, 66(Suppl 3), p. iii70-6. doi: 10.1136/ard.2007.078519.

Gonzalez-Rey, E., Chorny, A., Fernandez-Martin, A., Ganea, D. and Delgado, M. (2006) "Vasoactive intestinal peptide generates human tolerogenic dendritic cells that induce CD4 and CD8 regulatory T cells.," *Blood*, 107(9), pp. 3632–8. doi: 10.1182/blood-2005-11-4497.

Gonzalez-Rey, E. and Delgado, M. (2006) "Therapeutic treatment of experimental colitis with regulatory dendritic cells generated with vasoactive intestinal peptide.," *Gastroenterology*, 131(6), pp. 1799–811. doi: 10.1053/j.gastro.2006.10.023.

Gonzalez-Rey, E., Fernandez-Martin, A., Chorny, A., Martin, J., Pozo, D., Ganea, D. and Delgado, M. (2006) "Therapeutic effect of vasoactive intestinal peptide on experimental autoimmune encephalomyelitis: down-regulation of inflammatory and autoimmune responses.," *The American journal of pathology*, 168(4), pp. 1179–88. doi: 10.2353/ajpath.2006.051081.

Groneberg, D. A., Hartmann, P., Dinh, Q. T. and Fischer, A. (2001) "Expression and distribution of vasoactive intestinal polypeptide receptor VPAC(2) mRNA in human airways.," *Laboratory investigation; a journal of technical methods and pathology*, 81(5), pp. 749–55.

Herman, S., Krönke, G. and Schett, G. (2008) "Molecular mechanisms of inflammatory bone damage: emerging targets for therapy.," *Trends in molecular medicine*, 14(6), pp. 245–53. doi: 10.1016/j.molmed.2008.04.001.

Jimeno, R., Leceta, J., Martínez, C., Gutiérrez-Cañas, I., Carrión, M., Pérez-García, S., Garín, M., Mellado, M., Gomariz, R. P. and Juarranz, Y. (2014) "Vasoactive intestinal peptide maintains the nonpathogenic profile of human th17-polarized cells.," *Journal of molecular neuroscience : MN*, 54(3), pp. 512–25. doi: 10.1007/s12031-014-0318-3.

Laburthe, M. and Couvineau, A. (2002) "Molecular pharmacology and structure of VPAC Receptors for VIP and PACAP.," *Regulatory peptides*, 108(2–3), pp. 165–73.

Laburthe, M., Couvineau, A. and Marie, J. C. (2002) "VPAC receptors for VIP and PACAP.," *Receptors & channels*, 8(3–4), pp. 137–53.

McCulloch, D. A., Lutz, E. M., Johnson, M. S., MacKenzie, C. J. and Mitchell, R. (2000) "Differential activation of phospholipase D by VPAC and PAC1 receptors.," *Annals of the New York Academy of Sciences*, 921, pp. 175–85.

Mutt, V. (1988) “Vasoactive intestinal polypeptide and related peptides. Isolation and chemistry.,” *Annals of the New York Academy of Sciences*, 527, pp. 1–19.

Ottaway, C. A. (1987) “Selective effects of vasoactive intestinal peptide on the mitogenic response of murine T cells.,” *Immunology*, 62(2), pp. 291–7.

Ottaway, C. A. and Greenberg, G. R. (1984) “Interaction of vasoactive intestinal peptide with mouse lymphocytes: specific binding and the modulation of mitogen responses.,” *Journal of immunology (Baltimore, Md. : 1950)*, 132(1), pp. 417–23.

Persson, E. and Lerner, U. H. (2005) “The neuropeptide VIP potentiates IL-6 production induced by proinflammatory osteotropic cytokines in calvarial osteoblasts and the osteoblastic cell line MC3T3-E1.,” *Biochemical and biophysical research communications*, 335(3), pp. 705–11. doi: 10.1016/j.bbrc.2005.07.135.

Said, S. I. and Mutt, V. (1970) “Polypeptide with broad biological activity: isolation from small intestine.,” *Science (New York, N.Y.)*, 169(3951), pp. 1217–8.

Schwartz, C. J., Kimberg, D. V., Sheerin, H. E., Field, M. and Said, S. I. (1974) “Vasoactive Intestinal Peptide Stimulation of Adenylate Cyclase and Active Electrolyte Secretion in Intestinal Mucosa,” *Journal of Clinical Investigation*, 54(3), pp. 536–544. doi: 10.1172/JCI107790.

Söder, O. and Hellström, P. M. (1987) “Neuropeptide regulation of human thymocyte, guinea pig T lymphocyte and rat B lymphocyte mitogenesis.,” *International archives of allergy and applied immunology*, 84(2), pp. 205–11.

Tang, H., Sun, L., Xin, Z. and Ganea, D. (1996) “Down-regulation of cytokine expression in murine lymphocytes by PACAP and VIP.,” *Annals of the New York Academy of Sciences*, 805, pp. 768–78.

Tang, S. C., Braunsteiner, H. and Wiedermann, C. J. (1992) “Regulation of human T lymphoblast growth by sensory neuropeptides: augmentation of cholecystokinin-induced inhibition of Molt-4 proliferation by somatostatin and vasoactive intestinal peptide in vitro.,” *Immunology letters*, 34(3), pp. 237–42.

Verner, J. V and Morrison, A. B. (1958) “Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia.,” *The American journal of medicine*, 25(3), pp. 374–80.

Wang, H. Y., Xin, Z., Tang, H. and Ganea, D. (1996) "Vasoactive intestinal peptide inhibits IL-4 production in murine T cells by a post-transcriptional mechanism.," *Journal of immunology (Baltimore, Md. : 1950)*, 156(9), pp. 3243–53.

Yadav, M. and Goetzl, E. J. (2008) "Vasoactive intestinal peptide-mediated Th17 differentiation: an expanding spectrum of vasoactive intestinal peptide effects in immunity and autoimmunity.," *Annals of the New York Academy of Sciences*, 1144(1), pp. 83–9. doi: 10.1196/annals.1418.020.

Yadav, M., Huang, M.-C. and Goetzl, E. J. (2011) "VPAC1 (vasoactive intestinal peptide (VIP) receptor type 1) G protein-coupled receptor mediation of VIP enhancement of murine experimental colitis.," *Cellular immunology*, 267(2), pp. 124–32. doi: 10.1016/j.cellimm.2011.01.001.

Yadav, M., Rosenbaum, J. and Goetzl, E. J. (2008) "Cutting edge: vasoactive intestinal peptide (VIP) induces differentiation of Th17 cells with a distinctive cytokine profile.," *Journal of immunology (Baltimore, Md. : 1950)*, 180(5), pp. 2772–6.

Yin, H., Cheng, H., Yu, M., Zhang, F., Lin, J., Gao, Y., Han, B. and Zhu, L. (2005) "Vasoactive intestinal peptide ameliorates synovial cell functions of collagen-induced arthritis rats by down-regulating NF-kappaB activity.," *Immunological investigations*, 34(2), pp. 153–69.

Wussten Sie, dass **ACAD WRITE ®** bei Trustpilot mit dem Prädikat **„Hervorragend“** bewertet wird?

www.acad-write.com