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Hypothesis: VPAC G protein-coupled receptors for vasoactive intestinal peptide constitute a dynamic system for signaling T cells from plasma membrane and nuclear membrane complexes

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Abstract

The vasoactive intestinal peptide (VIP)-$VPAC_1$ and $VPAC_2$ G protein-coupled receptor (GPCR) systems are autocrine and paracrine regulators of diverse T cell functions. It has been recognized that VIP evokes two types of T cell responses. The first are rapid in onset and brief in duration, such as altered traffic in blood, lymphoid corridors, and tissues. The second are slow in onset and sustained in duration, such as enhanced helper T cell (Th) differentiation in the thymus and increased survival in lymphoid tissues with biases favoring the Th2-type effector and memory subsets. Investigations of some other sets of GPCRs for peptide and lipid mediators have demonstrated expression both in nuclear membranes and plasma membranes with respective linkages to responses that are slow in onset and sustained, and those that are rapid in onset and brief in duration. The hypothesis presented in this paper suggests that plasma membrane VPAC receptors transduce short-term effects of exogenous VIP on T cell effector functions, whereas nuclear VPAC receptors mediate endogenous VIP alterations in differentiation, proliferation, and survival. The types of substantial additional proof needed to support this hypothesis are described, as are its advantages for more selective VIP-directed therapies.

Keywords: Neuroendocrine peptide; Nuclear receptor; G proteins; Immune system; Inflammation

Contents

1. The vasoactive intestinal peptide (VIP)-$VPAC_1$/$VPAC_2$ G protein-coupled receptor (GPCR) axes in T cells

Most T cells produce and secrete authentic VIP at a level that increases after stimulation of the T cells by diverse mechanisms [1,2]. Some subsets of T cells such as type 2 helper T cells, termed Th2, generate far more VIP than other T cells, although these synthetic pathways are not well-defined [3]. The amount of VIP in lymphoid organs, including that stored in cholinergic and sensory nerves as well as in immune cells, is as functionally

Abbreviations: VIP, vasoactive intestinal peptide; GPCR, G protein-coupled receptor; $VPAC_1$, type 1 VIP receptor; $VPAC_2$, type 2 VIP receptor; T cell, T lymphocyte; LPA, lysophosphatidic acid; S1P, sphingosine 1-phosphate; LPA1, type 1 LPA receptor; iNOS, inducible nitric oxide synthase; COX-2, type 2 cyclooxygenase; MAP kinase, mitogen-activated protein kinase; ERK, extracellular signal-regulated type of MAP kinase; PKA, protein kinase A; TCR, T cell antigen receptor.

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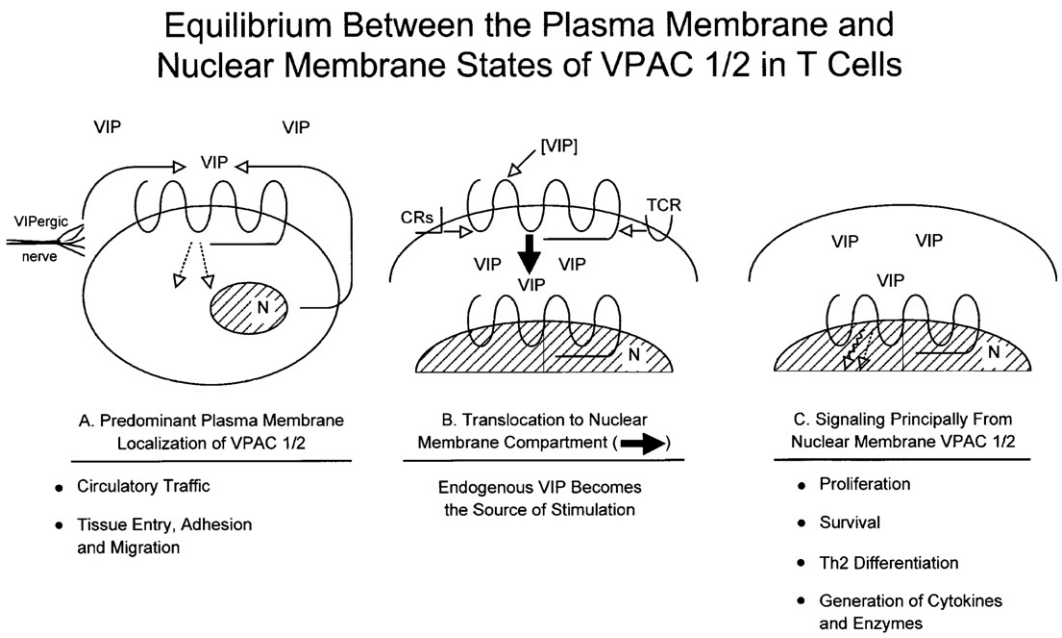

Fig. 1. Equilibrium between the plasma membrane and nuclear membrane states of $VPAC_{1/2}$ in T cells. A variety of stimuli encompassing VIP, ligands for a range of cytokine and chemokine receptors (CRs), and antigens that engage the T cell antigen receptor (TCR), evoke translocation (B) of plasma membrane VPAC receptors (A) to membranes of the nucleus (N) (C). Endogenous VIP activates VPAC receptors of the nuclear membranes and thereby elicits prolonged responses involving transcriptional events (C). The effector responses to extracellular VIP derived from neural and T cell sources are immediate and brief (A).

relevant as that recoverable from the central nervous system and endocrine organs. Although the gastrointestinal system also has high levels of VIP, the respective contributions of neural and immune sources there have not been resolved definitively. Rodent unstimulated T cells from several sites express predominantly type 1 VIP receptor ($VPAC_1$) and many types of stimulation reduce T cell expression of $VPAC_1$ while increasing very significantly the expression of type 2 VIP receptor ($VPAC_2$) [4–6]. Human blood T cells express higher levels of $VPAC_1$ than $VPAC_2$ before specific stimulation, but both types are represented at levels capable of transducing signals unlike the $VPAC_1$-dominant repertoire in rodent unstimulated T cells [7]. Nonetheless, stimulation of human blood T cells in several ways decreases their expression of $VPAC_1$ and increases that of $VPAC_2$. VPAC Rs also are expressed by macrophages, dendritic cells, and mast cells in the immune system [8,9].

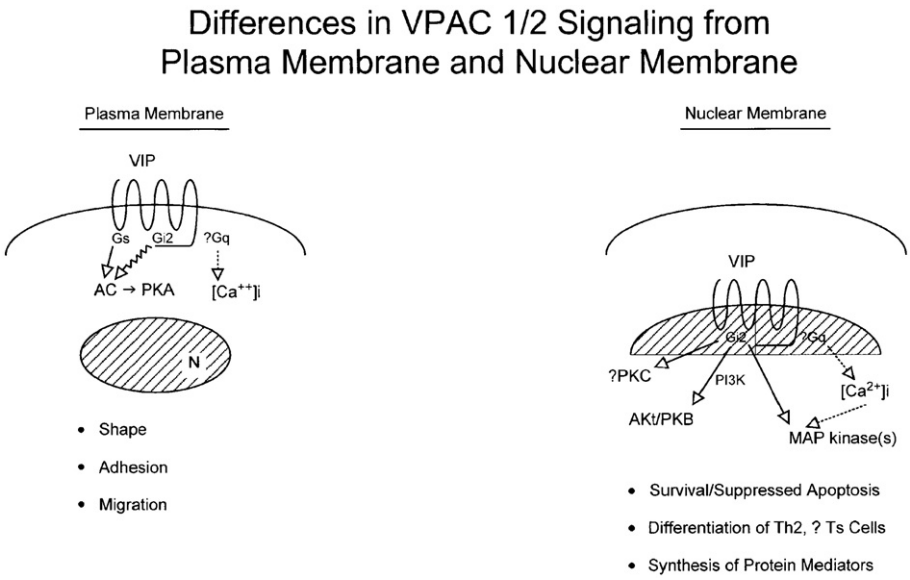

Fig. 2. Differences in $VPAC_{1/2}$ signaling from plasma membrane and nuclear membrane sites. Plasma membrane signals require coupling to Gs and Gq to affect both [cAMP]i and $[Ca^{2+}]i$. Nuclear membrane signals depend on a more complex set of interactions with Gi2 to recruit a range of kinases coupled to proliferation and survival, as well as with Gq to increase $[Ca^{2+}]i$ that permits activation of MAP kinases.