

Speculations around the Mechanism behind the Action of Peptide T in the Healing of Psoriasis: A Minireview

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Peptide T, the HIV envelope-derived fragment Ala-Ser-Thr-Thr-Thr-Asn-Tyr-Thr, has already been used to successfully treat psoriatic patients without major side-effects. The underlying reason for the positive effect is, however, at present unknown. In the following minireview, we summarize today's knowledge regarding peptide T's interaction with other chemical messenger molecules, such as somatostatin, vasoactive intestinal polypeptide (VIP) and epidermal growth factor (EGF), within the human skin, and, finally, speculate about their relationship to each other. In summary, we believe that the clearance effect of peptide T on psoriasis will open up new avenues with regard to the concept of the pathogenesis of as well as the clinical attendance to this disease. Key words: Somatostatin; Vasoactive intestinal polypeptide; Epidermal growth factor.

(Accepted May 10, 1993.)

Acta Derm Venereol (Stockh) 1993; 73: 401-403.

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Peptide T (Ala-Ser-Thr-Thr-Thr-Asn-Tyr-Thr) has been used with positive treatment effects in a high proportion of psoriatic patients (1-3). The mechanism through which peptide T works is at present unknown; however, it has been suggested that peptide T acts by blocking the CD4 receptor, thus preventing the penetration of a putative psoriasis-causing retrovirus (4) which is an assumed ligand for the CD4/T4 receptor. On the basis of sequence similarity, chemotactic bioassays, competitive bindings studies and similarities of CD4 and vasoactive intestinal polypeptide (VIP) receptor distributions in monkey brain (5-10), it has been proposed that the HIV envelope protein gp 120 (gp 120) and VIP may compete for the same or similar receptors. VIP also has the same preventing effect on induced neuronal death by gp 120 as peptide T itself (11).

Since we believe that the clearance effect of peptide T on psoriasis in a high proportion of cases will open up new avenues with regard to the concept of the pathogenesis, we would like to speculate on possible mechanisms on the basis of the relationship between peptide T and VIP. The most interesting question is what mechanisms are involved in the beneficial effects of peptide T in psoriatic patients. If we could find out peptide T's action, maybe we would come one step further in our understanding of the pathogenesis of this disease. With respect to findings in other parts of the body some speculations can be made.

In 1986 Farber et al. (12) proposed, on the basis of the temporal onset of psoriasis eruptions following "emotional

stress" and the symmetrical lesions in untreated patients, that the nervous system and its neuropeptides might be involved in the etiopathogenesis of psoriasis. Increased levels of substance P and VIP (13,14), arachidonic acid metabolites (15), polyamines (16) and calmodulin (17) in lesional psoriatic skin suggest that both neuropeptides and other inflammatory mediators may play an important role. The significantly elevated tissue levels of VIP according to radioimmunoassay data did not, however, parallel immunohistochemical data in a recent study by Eedy and collaborators (13). The discrepancy between the radioimmunoassay data and the immunohistochemical analyses is in agreement with earlier investigations (18-20) as well as with recent data from our laboratory (unpublished) in support of the immunohistochemical part of the study by Eedy et al., showing no pattern changes in the nerve fibre population, neither between normal, non-lesional and lesional skin, nor during peptide T treatment of psoriatic patients. It is still therefore reasonable to assume that changes in levels of VIP are possible also during peptide T infusions even if we did not detect any distribution or staining intensity changes. Radioimmunoassay measurements have, unfortunately, not yet been performed in patients during peptide T treatment.

In the following, our discussion is summarized using the diagram (Fig. 1A) of Zandomenighi et al. (21) from their study of duodenal tissue cultures. Since psoriatic patients have elevated skin tissue levels of VIP, one possible reason for psoriatic hyperproliferation could be a VIP influence on epidermal growth factor (EGF) or other growth factors. It has been reported that VIP significantly increases EGF levels in duodenal tissue biopsy cultures (21). Peptide T has been proposed to work via the same receptors as VIP (10). If this is true also for peripheral cell systems, peptide T could competitively block the effects of increased VIP levels; thus the higher levels of EGF assumed to be induced by VIP could then be prevented (cf. Fig. 1B). Additionally, especially if autoreceptors are involved, this could increase the levels of free VIP in the tissue and lead to negative feedback effects, maybe mediated by somatostatin (SOM) which in turn regulates the EGF levels (21) (cf. Fig. 1C). This could very well be in line with our newly described findings of increase and decrease of SOM during peptide T treatment of psoriasis (22) and the reports of good antiproliferative effects of SOM infusion in psoriasis (23). However, some evidence has been put forward that, at least in the gastrointestinal tract as well as in the pineal gland, there is a lack of interaction between peptide T and the VIP receptor (24, 25). This could naturally also be true for the skin.

Furthermore, systemic changes in levels of important sub-

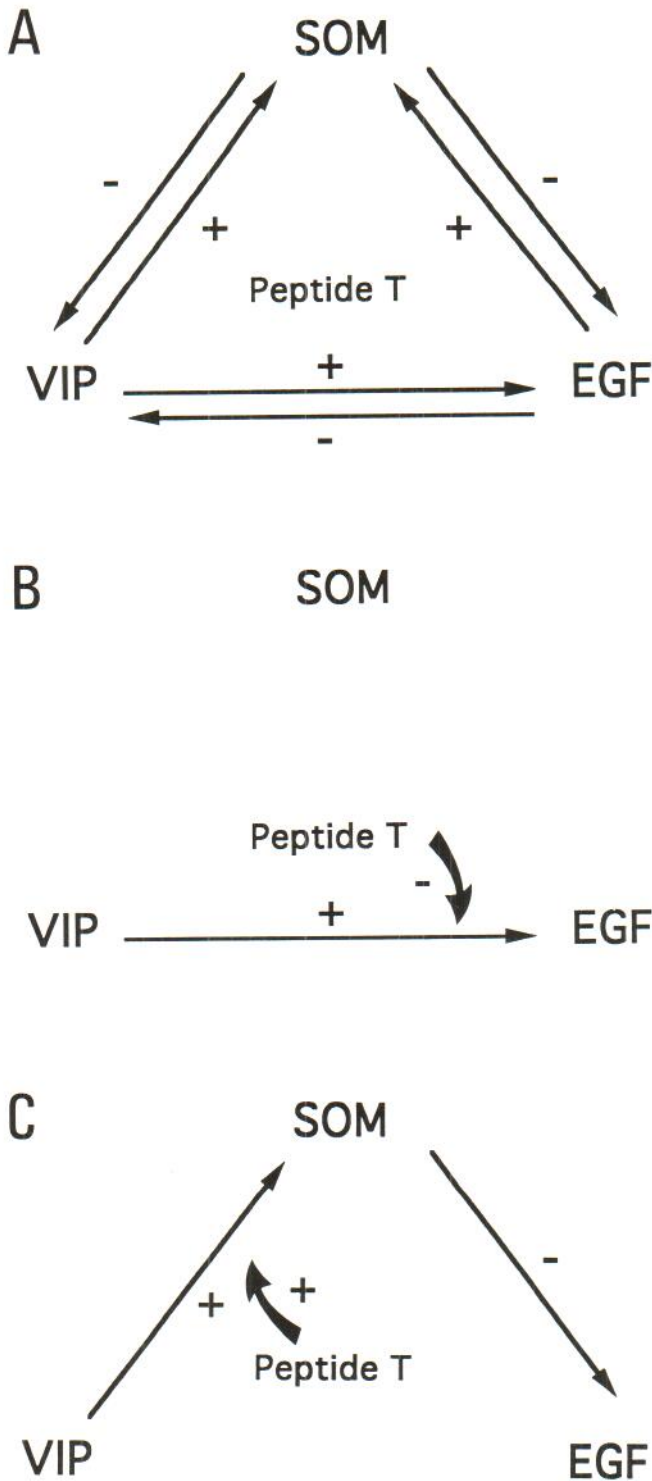


Fig 1. (A) Schematic illustration summarizing the possible interactions between peptide T, vasoactive intestinal polypeptide (VIP), somatostatin (SOM) and epidermal growth factor (EGF) in the healing of psoriasis. (B) Receptor interaction(s) by peptide T preventing VIP-induced increase in EGF levels. (C) Peptide T-dependent increase in free VIP levels, consecutively leading to a SOM-mediated decrease of EGF levels. See text for further explanations. Adapted from Zandomenighi et al. (21).

stances can be involved in the skin changes during peptide T treatment. Since psoriatic skin has more EGF receptors (26), "normal" levels of EGF can lead to increased biological effects. VIP and EGF plasma levels are reported not to be changed in psoriasis (13,23). The infusion of SOM has been reported to give decreased EGF levels in blood (23). Such a decreased EGF content could therefore stabilize the epidermal proliferation in psoriasis. Vernier et al. (23) also reported decreased plasma levels of growth hormone (GH) during SOM infusion. It must be considered of great importance to measure systemic levels of EGF, GH as well as of SOM and VIP during peptide T infusions in future investigations.

If the hypothesis of a viral component in the etiopathogenesis of psoriasis is considered, it is possible that, again, blocking of receptors may be involved. It is a possible mechanism since VIP, antibodies to mouse CD4 and peptide T itself can prevent gp 120-induced neuronal death in hippocampal cultures that have established synaptic connectivity. Furthermore, peptide T and its analogues can prevent gp 120-induced neuronal cell death at low concentrations (11,27). Infection by a putative psoriasis-causing retrovirus could be prevented by blocking the receptors of the cells to be targets for such an infection.

Normal epidermal proliferation has been proposed to be regulated by a growth-inhibitory epidermal pentapeptide (28). This must be taken into consideration when it comes to hyperproliferative diseases. If psoriatic skin lacks or has reduced levels of this regulatory substance, peptide T treatment could induce a replacement inhibitor. Maybe the above-mentioned SOM could fulfil this task, as SOM is known to be a powerful inhibitor in many systems.

It is obvious that peptide T, especially in conjunction with psoriasis, has to be investigated further. The treatment effects seem to be considerable, which perhaps can help patients taking a short view, and studies of this substance and its interactions with the body could teach us more about the pathogenesis and the etiology of this disease, enabling us to create more effective medicines with fewer side-effects or even prevent the disease.

ACKNOWLEDGEMENTS

This work was supported by grants from Edvard Welanders Stiftelse, Svenska Psoriasisförbundet, IngaBritt och Arne Lundbergs Forskningsstiftelse, Torsten och Ragnar Söderbergs Stiftelser, and funds from the Medical Faculty of the Karolinska Institute. Dr. M. Virtanen is gratefully acknowledged for expert help with the illustration.

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