

Synthesis, characterization, and conformation of highly potent headache-inducing peptides

Chomal E. Cap,¹ Jaimal Alatéte, Jr.,² and Dolores de Cavezas³

¹*Magic Pharmaceuticals, St. Louis, MO 63121, U.S.A.*; ²*Department of Chemistry and Biochemistry, Univ. Paris 18, 75005 Paris, France*; and ³*Department of Physiology of Any Headache, San Bernardino State College, Port Prince, H-2175 Haiti*

Introduction

Ongoing studies from our laboratories [1] challenge the pioneering work of other research units [2] on the factors and mechanism of generation of headache in stressed people such as top managers, executives, chairmen of meetings with large attendance, etc.. While these earlier authors correctly proposed tentatively a role for compounds of peptidic origin in these processes, the analytical techniques at their disposal were insufficiently sensitive to show that these compounds are indeed peptides, which are mainly produced when a combination of factors are involved such as stress from hard and intense working life or/and poor life conditions, coupled with bad weather conditions and unpleasant living environment.

Results and Discussion

A high affinity endogenous ligand was isolated from the blood of 120 volunteers suffering of severe and almost incurable headache. Samples were collected daily over a period of 4 months. The material was identified by an assay involving fluorescently-tagged cloned enkephalin receptors, and the chemical structure was determined by Non Outstanding Experimental Spectroscopy (NOESY) NMR coupled with Computer Assisted Chemical Compound Assignment (CACCA method) as an enkephalin-bound peptide as given in Fig. 1. The purified material was found to induce strong headache, depression, or in some cases even aggression [3] depending on the type of visual and/or audio stimulation and in general on the environment and weather conditions when used on three volunteer teams living in different geographical environments. The proposed structure was confirmed by unambiguous chemical synthesis.

The affinities of the natural and the synthetic compounds were compared, and found to be similar within experimental error (Table 1). Affinities were strongly dependent on the team provenience. Interestingly, binding efficacy was independent of the concentration

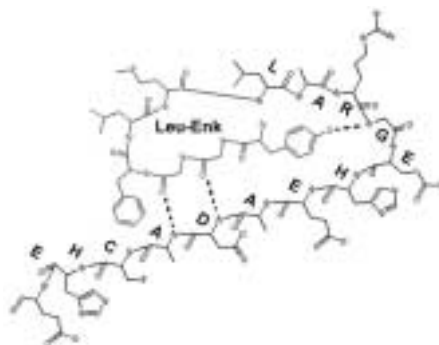


Fig. 1. Structure of headache-inducing peptide

of exogenous euphoria-inducing material such as for example alcohol intake, although in most cases it did help in inducing sleep and rest.

Table 1. Activity of the headache-inducing peptide as determined on three team samples (each of 50 persons).

Team	Affinity (M)	
	Natural ligand	Synthetic ligand
People from Large Cities	$2.4 \pm 0.6 \times 10^{-4}$	$2.7 \pm 0.5 \times 10^{-4}$
People from Small Villages	$1.4 \pm 0.3 \times 10^{-6}$	$1.5 \pm 0.4 \times 10^{-6}$
People from Polynesia	$3.4 \pm 1.6 \times 10^{-8}$	$3.2 \pm 1.5 \times 10^{-8}$

Studies currently in progress involve combinatorial synthesis of analogues of the natural compound. The ultimate goal of this research is a deeper understanding of the structure activity relationships in order to identify the mode of interactions of these peptides with the enkephalin receptor, making thus possible the preparation of compounds which by strongly interacting with the headache-inducing peptides could inhibit their binding to the receptor. Interestingly enough it was discovered [4] that volunteers affected by this disease were able to improve their miserable condition in living at least for a week in places like the Hawaii, the Maldives or the Mauritius Islands. Apparently in these places the environmental conditions allow for a more rapid hydrolysis of the headache-inducing peptide with release of enkephalin which having stronger affinity for the receptor induces pleasant feelings and a relaxed condition.

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