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Endomorphin-2 Derivatives: Rapid Relief of Various Pains by Topical Administration or by Superficial Local Injection

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Abstract

Background and purpose: Endomorphin-2 is a physiologic tetrapeptide amide, Tyr-Pro-Phe-Phe-NH_2, which has been shown to provide an analgesic effect in mice and rats by injection into the brain. In our previous report, we showed that certain Endomorphin-2 derivatives, such as N-Ac-Tyr-Pro-Phe-Phe-NH_2 could provide instant analgesia on topical application. The case reports presented herein reveal that a number of N-substituent radicals enhance analgesic effects of the derivative applied topically or injected subcutaneously near the site of pain.

Approach to find efficacious molecules: Various endomorphin-2 derivatives have been synthesized, including N-Ab-Tyr-Pro-Phe-Phe-NH_2, N-Bo-Tyr-Pro-Phe-Phe-NH_2, N-Pc-Tyr-Pro-Phe-Phe-NH_2, and test solutions containing the derivatives were formulated. Toxicology tests were done on all the synthesized derivatives in mice by subcutaneous injections.

Note: Ab, 2-acetoxybenzoyl (Aspirin radical); Bo, benzyloxycarbonyl; Pc, phenyl acetyl.

Results and Discussions: All the synthesized derivatives are safe in mice studies up to 100 mg/kg by subcutaneous injections. All the test solutions containing 1%–3% of the above derivatives have been found to instantly relieve various pains, and to last for more than 7 hours on topical application. Certain derivatives have also been found to rapidly relieve vertebral pain after subcutaneous injections at a concentration of 3.75 mg/0.5 ml for each injection. Animal studies have shown that in contrast to morphine or other opiates, endomorphin-2 does not have any addiction properties.

Implications: There are no issues of addiction, toxicity, or adverse reactions known with the endomorphin-2 derivatives such as N-2-acetoxy benzoyl-endomorphin-2, N-phenyl acetyl-endomorphin-2, and N-benzyloxycarbonyl-endomorphin-2. They can be used instead of morphine or other opiates for pain control in numerous conditions.

Introduction

Animal studies have found that two endogenous tetrapeptide amides, endomorphin-1 and endomorphin-2, have an analgesic effect when systemically administered by injection into the brain of mice or rats [1–3]. However, human studies have shown that only endomorphin-2 and its derivatives but not endomorphin-1 or its derivatives have any substantial analgesic effect by systemic administration [4].

Human studies also revealed for the first time that endomorphin-2

and its derivatives but not endomorphin-1 or its derivatives could rapidly relieve various pains after topical administration [4]. Because endomorphin-1 with Tyr-Pro-Trp-Phe-NH_2 has a different tetrapeptide sequence than endomorphin-2 with Tyr-Pro-Phe-Phe-NH_2, it may explain the difference in analgesic effect between animal and human subjects.

Due to a slight difference in peptide structure, endomorphin-2 and endomorphin-1 also has a different receptor glycoprotein, namely mu 1 (μ1) and mu 2(μ2), respectively [1–3]. The neuro-anatomical distribution of endomorphins in animal studies reflects their potential endogenous role in many major physiological processes; these include

(a) Perception of pain.
(b) Responses related to stress. and
(c) Complex functions such as reward, arousal, and vigilance, as well as autonomic, cognitive, neuro-endocrine, and limbic homeostasis [5,6].

The present clinical results suggest that changing the N-Terminal radical can provide better bind to the receptor molecule and provide a longer-lasting analgesic effect [7].

Case Presentation 1

Female, age 59, had lower back pain for many years. The pain was related to her work as a personal caregiver. The pain started the early afternoon of her workday and became very aggravating at the end of the workday. She had used numerous over-the-counter anti-pain medications, including aspirin and Motrin, but without much relief.

Method

Test solution: Endomorphin-2 derivative, N-Pc-Tyr-Pro-Phe-Phe-NH_2, white crystal 3 grams was dissolved in a 97 ml solution prepared from water 40 parts, ethanol 40 parts and propylene glycol 20 parts by volume (from now on as WEP442). The solution thus prepared contained the derivative 3% in WEP442.

Note: Pc: Phenyl Acetyl.

Results

The subject was instructed to topically apply the solution to her lower back with a sufficient solution to wet the skin thoroughly. The subject reported that her lower back pain disappeared within 5 minutes of topical application and was pain-free for the next 14 hours.

The same analgesic effect was obtained daily by the same procedure with her back relived for 12 hours–14 hours throughout a two week evaluation time.

Case Presentation 2

Female, age 60, had psoriasis for about four decades and worsening psoriatic arthritis over the past decade, with the involvement of fingers, wrists, and ankles. She has used numerous over-the-counter anti-pain medications, including aspirin and Motrin, but without much relief of pain.

Method

Test solution: Endomorphin-2 derivative, N-Ab-Tyr-Pro-Phe-Phe-NH_2, white crystals 1 gram of which was dissolved in 99 ml of a solution prepared from water 40 parts, ethanol 40 parts and propylene glycol 20 parts by volume. The test solution thus prepared contained the derivative 1% in WEP442.

The subject was instructed to topically apply this solution to her fingers, wrists, and ankles with a sufficient amount of solution to wet the skin thoroughly.

Results

The subject reported that pain in her fingers, wrists, and ankles disappeared within 5 minutes of topical application. All areas were pain-free for the next 7 hours.

The same analgesic effects were obtained daily by the same procedure over a one week evaluation time.

Case Presentation 3

Female, age 58, with recurrent severe headaches recently diagnosed by a neurologist as migraine headaches, experienced one such headache at mid-morning. With this headache was the concurrent sensation if intense pressure being applied to her head.

Method

Test solutions: Test solution A; endomorphin-2 derivative, N-Ab-Tyr-Pro-Phe-Phe-NH_2, white crystals 1 gram of which was dissolved in 99 ml of the solution prepared from water 40 parts, ethanol 40 parts and propylene glycol 20 parts by volume. Test solution A thus prepared contained the derivative, 1% in WEP442. The Test solution B contained the derivative 3% in WEP442, prepared in the same way except the derivative 3 grams was dissolved in 97 ml solution.

The subject topically applied to her forehead and temporal areas Test solution A and Test Solution B as described below.

Results

The subject reported that there was no relief of symptoms after the topical application of Test solution A. At about 20 minutes after this topical application, the subject took one tablet of hydrocodone-acetominophen 5-325 mg, which provided no detectable relief of pain nor pressure symptoms over the ensuing hour. At that time, subject topically applied to the forehead and temporal areas the Test solution B. She reported that all symptoms abruptly and completely ceased within 1–2 minutes of topical application. During sleeping hours, that night after midnight, the subject was awakened by a sense of recurrent head pain, after which she again applied Test solution B. All sensation of pain abruptly ceased. The

next day on two occasions, the onset of recurrent head pain was detected; the subject again applied the Test solution B with prompt relief of any sense of pain. No sense of the return of symptoms was experienced over the next week.

The above results show that while the Test solution at 1% concentration did not provide any detectable analgesic effect, the Test solution B at 3% concentration did give prompt relief of migraine pain in this individual.

Case Presentation 4

A female, age 61, had osteoarthritis of the left hip and right knee, which began about three years earlier with pain occurring episodically, associated with being on her feet for long periods. Treatment with oral ibuprofen was found to provide relief of pain over the course of about two years, but had failed to give sufficient relief in recent months; nor had topical Over–The–Counter (OTC) remedies provided significant additional benefit.

Method

Since the symptoms of pain were not constant, worsening either in association with weather conditions and/or physical stress from household working activities, no fixed schedule of testing was feasible. Thus, topical applications of test solution were initiated when an episode of pain emerged. The test solution was N-Bo-Tyr-Pro-Phe-Phe-NH_2, 2% in WEP442.

Note: BO: Benzyl Oxycarbonyl.

Results

The subject topically applied Test solution to the painful left hip and right knee as needed. The pains in her left hip and right knee disappeared after 5 minutes of topical application and lasted for 7–8 hours on repeated occasions over a 4 week evaluation time.

Case Presentation 5

Female, age 62, with spinal osteoarthritis involving vertebrae C6, C7 and T1. She related this condition to trauma sustained in a bicycle accident in her teen years. The onset of pain in this spinal area occurred at about age 50, becoming progressively painful and disabling. The pain was not being relieved finally by oral NSAIDS.

Method

Test solution: N-Ab-Tyr-Pro-Phe-Phe-NH_2, white crystals, 0.75 grams of which was dissolved in a vehicle comprised of lidocaine 0.1; propylene glycol 5; water 94.9 to make a 0.75% (w/v) solution (7.5 mg/ml). This solution, 0.5 ml (3.75 mg), was subcutaneously injected into each of 2 painful sites, 1.5 cm to the right of involved vertebral joints.

Result

Complete pain relief occurred within 1–2 minutes. At the time of observation three weeks later, the affected areas remained pain-free.

Case Presentation 6

Female, age 57, presented with spontaneous tic movements of the head and sharp pain at punctate sites of the right upper back, medically diagnosed as cervical dystonia symptoms. The subject had been under neurological treatment that included injections of Botox at multiple sites (left neck, right neck, posterior right scalp and upper right back). This treatment eradicated the head's tic movements but was associated with worsening of the sharp pain at punctate sites of the right upper back.

Method

Test solution: N-Ab-Tyr-Pro-Phe-Phe-NH_2, white crystals dissolved in a vehicle comprised of lidocaine, 0.25 grams: propylene glycol 5 ml: water 94.75, to make a 0.75% (7.5 mg/ml) solution. At each of five pain sites, 0.5 ml (3.75 mg) of the solution was injected at subcutaneous depth.

Note: As, 2-acetoxybenzoyl; PG: Propylene Glycol.

Result

Almost instantaneously, pain at each site ceased. Sites remained pain-free for 7–8 days.

These findings indicate that certain derivative of the peptide can perform as an efficacious anti-pain agent when injected into pain sites.

Case Presentation 7

Male, age 97, had osteoarthritis of vertebral joints involving vertebrae C4–C7 and T1–T5, with an extruded intervertebral cervical disc at vertebrae 6–7, radiologically diagnosed several years earlier. Previous therapy undergone by the subject included epidural injections of corticosteroids. Within the past several months, the pain had intensified, along with a substantial degree of paresthesia and numbness of the fingers of both hands.

Method

Test solution: N-Ab-Tyr-Pro-Phe-Phe-NH_2, white crystals 0.75 gram was dissolved in a vehicle comprised of lidocaine 0.1grams: propylene glycol 5ml: water 94.9 ml to make a 0.75% (7.5 mg/ml) solution. Subcutaneously, over very painful sites about 1.5 cm to the right of the midline of the spine, 0.5 ml of the solution was administered via a tuberculin syringe with 27-gauge needle.

Result

Complete relief of pain occurred within 10–15 minutes.

Injected sites remained pain-free for about two weeks. At three weeks, spinal pain had returned at a very disturbing intensity, involving vertebral sites at C4, 5, 6, 7 and T1, 2, 3, 4, 5. Subcutaneous injection of 0.2 ml of the solution was made in the space between spinal processes of C5–6, C6–7, C7–T1, T1–T2, T2–T3, and T3–T4. Complete relief of pain at all injected sites occurred within about 20 minutes and lasted for about eight weeks.

Receptors and Mechanism of Action

The mechanism of drug action refers to the biochemical process through which a drug produces its pharmacological effect by binding to a receptor molecule—the receptor molecule is usually located on the surface of cells or otherwise in the tissues. After binding, the drug and receptor complex can induce cell activity and produce pharmacological and therapeutic effects.

Specificity of Drug Molecule

Most drugs bind to a specific type of receptor and are referred to as receptor selectivity or specificity. The ability of a drug to bind to a certain receptor is based on its unique chemical structure. For example, endomorphin-2 binds to its specific receptor, mu (μ), to produce an analgesic effect in the brain of mice or rats. It is also known that the mu receptor is a glycoprotein.

We speculate that the receptor molecule is present in the epidermal nerve endings in the human skin; Subcutaneous levels.

We believe the analgesic potency of an endomorphin-2 derivative depends on how tight the binding is between the derivative and its receptor protein or glycoprotein; the tighter binding, the more potent. The binding affinity of the derivative depends on two radicals, namely, N-terminus and C-terminus substitutions. Because of the rapid analgesic effect after topical application to skin sites, we believe the receptor protein or glycoprotein is present in the nerve endings within the outer layers of the epidermis of the human skin.

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Contribution:

Ruey J Yu: Designed and formulated the derivatives; Eugene J Van Scott: Formulated and evaluated the derivatives.

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