



Could calcitonin be a useful therapeutic agent for trigeminal neuralgia?

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Summary Trigeminal neuralgia (TN) has been recognized as one of the most common neurovascular syndromes caused by the vascular contact of the trigeminal nerve in its root entry zone (REZ) with a branch of the superior or anterior inferior cerebellar arteries, leading to a demyelination of trigeminal sensory fibers within either the nerve root or, less commonly, the brainstem. There is a lack of certainty regarding the aetiology and pathophysiology of TN, therefore the treatment of trigeminal neuropathic pain disorders continues to be a major therapeutic challenge. The identification of novel therapeutic agents for the treatment of these disorders is important. Calcitonin (especially intranasal) provides an interesting analgesic effect in a series of painful conditions including reflex sympathetic dystrophy syndrome, adhesive capsulitis, ankylosing spondylitis, rheumatoid arthritis, vertebral crush fractures and metastasis, phantom limb pain, etc. Exogenous calcitonin is thought to cross the blood-brain barrier and to accumulate slowly in the brain, inducing analgesia once sufficient receptors are occupied. We hypothesize that calcitonin may have anti-trigeminal neuralgia properties. From the clinical point of use, the analgesic effect of calcitonin will be beneficial throughout the whole period of medical treatment of trigeminal neuralgia patients.

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Background

Analgesic effect of calcitonin

Calcitonin (CT) is a polypeptide hormone involved primarily in the regulation of blood calcium levels and bone calcium metabolism. A number of reviews have concluded that salmon calcitonin is safe and effective in the treatment of osteoporosis [1,2].

Additionally, the analgesic activity of salmon calcitonin (subcutaneous or intranasal) has been shown in several controlled prospective double-blind studies to improve pain [3,4]. However, the explanation of the analgesic effect of calcitonin is still not clear. A number of hypotheses have been advanced. An old observation is that inhibition of prostaglandin E2 synthesis as a result of an anti-inflammatory activity of calcitonin was also proposed as an explanation of its analgesic effect [5]. Interference with calcium flux, involvement of the cholinergic or serotonergic systems, stimulation of β -endorphin release is

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the other viewpoint. In humans, similarities between CT- and morphine-induced analgesia and reports of CT-induced elevation of plasma β -endorphin levels [4,5] suggest the possible involvement of the endogenous opiate system in mediating the analgesic action of CT. The possibility of a direct action on calcitonin receptors in the central neural system (CNS) seems to be an attractive hypothesis [6]. The demonstration of CT binding sites in areas of the brain involved in pain perception and a series of animal studies have raised the possibility that CT may directly modulate nociception in the CNS. Intracerebroventricular, but not subcutaneous, administration of salmon CT raises the pain threshold in rabbits, and this effect does not involve opiate receptors because it is not antagonized by naloxone, and appears to be sustained on repeated dosing. In a recently published study, Sibilia et al. [7] reported that specific binding sites for amylin and salmon calcitonin are present in the pons-medulla of rat brain.

The Analgesic effect of calcitonin in clinical application

Salmon calcitonin (especially intranasal) provides an interesting analgesic effect in a series of painful conditions including reflex sympathetic dystrophy syndrome, adhesive capsulitis, ankylosing spondylitis, rheumatoid arthritis, vertebral crush fractures and metastasis, phantom limb pain, etc. The majority of evidence of the analgesic activity of salmon calcitonin is derived from clinical studies in tumor metastasis, Paget's disease, osteoporosis fracture, and in animal models such as rabbits subjected to electrical stimulation of their dental pulp. Salmon calcitonin alone or in conjunction with conventional analgesic molecules appears to be a valuable additional approach for cancer patients with bone metastasis or myeloma responding poorly to conventional therapy, and for those for whom radiation is not appropriate. Their quality of life is also improved. Similarly, two patients with chronic nonmalignant pain experienced a benefit after intrathecal administration of calcitonin. In osteoporosis patients, the group treated with CT had significantly lower pain scores at each assessment than the group receiving placebo [8]. Epidural salmon calcitonin in combination with local anaesthetic produces an analgesic effect similar to fentanyl and with stable hemodynamic results. It also eliminates postoperative hyperglycaemia. This study shows that calcitonin is a suitable alternative for the treatment of acute postoperative pain [3]. Positive reports have been published of

the effect of salmon calcitonin in reducing phantom limb pain and painful diabetic neuropathy. In the first condition, TCT yielded in half of the patients a rapid (within 1 h) pain relief, which was sustained over 3 weeks. Interestingly, mammalian calcitonin appears less potent and less rapid than calcitonin from other species, and the nasal route appears better than the subcutaneous or intramuscular route, at least on the release of β endorphin, which is rapidly increased [4]. The osteoporosis patients receiving 200 IU of salmon CT nasal spray per day consumed significantly less analgesic per day than patients in the placebo group [8]. Also, from the experience with crush fractures, nasal salmon calcitonin spray (200 IU) shows greater pain relief than intramuscular injection (already within 7 days). The analgesic effect is associated with an elevation of the circulating levels of β endorphin, which seems to be higher with the nasal form.

Hypothesis

Trigeminal neuralgia (TN) is a rare form of neuropathic facial pain characterised by severe, paroxysmal pains in the face. There is a lack of certainty regarding the aetiology and pathophysiology of TN [9] and little is known about the decision process in treatment of TN, and management with anti-epileptic drugs or surgical procedures carries risks of side effects, recurrence and complications [10]. Decision analysis in the health care context combines evidence and helps to determine the optimal strategy under given circumstances [11,12]. Surgery for TN is either destructive (ablative) where the trigeminal nerve sensory function is intentionally destroyed, or non-destructive where the trigeminal nerve is decompressed, with normal function usually preserved. All surgeries carry risks of complications either in the immediate perioperative period or in the long term. There is also a very small risk of mortality for each of the treatments [13]. Medication is often a first line treatment [9,14]. Traditionally, it is only when medications fail or severe side effects develop that patients are offered surgical options [15]. However medical management with anti-convulsant (anti-epileptic) drugs carries debilitating side effects and the drugs eventually tend to lose effectiveness. The treatment of trigeminal neuropathic pain disorders continues to be a major therapeutic challenge and the identification of novel therapeutic agents for the treatment of these disorders is important. In the future, the research about calcitonin may offer an optimistic outlook for the therapy

of trigeminal neuralgia. We desire to see the patients suffering trigeminal neuralgia receiving salmon CT nasal spray per day and revealing a happy smile.

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