Capsaicin Application to the Temporomandibular Joint Alters Calcitonin Gene-Related Peptide Levels in the Trigeminal Ganglion of the Rat

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The aim of this investigation was to determine the temporal effect of an intra-articular injection of capsaicin to the temporomandibular joint on the levels of calcitonin gene-related peptide-like immunoreactivity (CGRP-ir) in the trigeminal ganglion of the rat. The temporomandibular joints of 26 adult female rats were injected on one side with capsaicin and contralaterally with a control vehicle. Another 8 animals served as an untreated control group and received no injections. Animals were sacrificed at time intervals of 4 hours, 48 hours, 10 days, and 21 days following treatment. The trigeminal ganglia were extirpated, and CGRP-ir levels were quantified using a radioimmunoassay. Results demonstrated that when the capsaicin-treated side and the vehicle-treated side were compared, CGRP-ir levels decreased initially at 4 hours and increased at 48 hours. At 10 days, CGRP-ir levels had again dropped below control levels, followed by an increase at 21 days. CGRP-ir levels for the first two time periods investigated, which simulate an acute inflammatory state, mimic results observed in studies using limb joints, while the other time periods, which represent an intermediate and a chronic condition, respectively, suggest a more complex interaction with capsaicin-sensitive primary afferents.

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Although many components of the peripheral and central pain pathways have been elucidated, a remedy for chronic pain has not yet been found. An area of particular concern is the temporomandibular joint (TMJ); it has been estimated that 10 to 15% of the general population has some manifestation of pain or inflammation at this joint, and that women are afflicted considerably more often than men.[1,2] However, few researchers have attempted to characterize the mediators involved in temporomandibular disorders (TMD). The focus of many studies of inflammation in limb joints has been to identify the role of particular mediators. Data from these studies suggest that the neuropeptide calcitonin gene-related peptide (CGRP) might be an important inflammatory agent.[3–6]

CGRP is a 37-amino acid polypeptide that is encoded and expressed by tissue-specific alternative splicing of ribonucleic acid (RNA) transcribed from the calcitonin gene.[7,8] Numerous investigations have demonstrated that CGRP is one of the most abundant neuropeptides, and that it is widely distributed throughout the central[8–12] and peripheral[13–17] nervous systems. Peripherally,

this neuropeptide is located within branches of sensory, gastrointestinal tract, and preganglionic autonomic neurons.[14] However, the highest levels of CGRP messenger RNA expression in the peripheral nervous system are located within the trigeminal ganglion.[18] Neurons containing CGRP represent 30 to 40% of all neurons within the trigeminal ganglion of the rat; small cells (less than 20 μm) represent 30% of the CGRP-containing cells, medium cells (20 to 30 μm) comprise 30%, and large cells (greater than 30 μm) make up 40% of the CGRP-containing neurons.[19,20]

CGRP has been postulated to mediate numerous actions, including vasodilation, inflammatory responses, and nociception, either by itself or through a modulatory effect on other agents such as substance P and histamine.[21–27] CGRP levels are significantly altered in the dorsal root ganglia[28–32] and spinal cord[28,30,33,34] following the induction of inflammation in limb joints.

Capsaicin (8-methyl-N-vanillyl-6-nonenamide), which has a unique pharmacologic ability to act selectively on specific neurons and fibers associated with nociception, has been extensively studied. Capsaicin stimulates polymodal nociceptive neurons with conduction velocities in the ranges of both C- and A-delta fibers.[35] The effects of capsaicin are exerted through the activation of specific receptors located on "capsaicin-sensitive primary afferents."[36,37] Initially, capsaicin-sensitive neurons are depolarized, but in the continued presence of capsaicin these neurons eventually lose their ability to depolarize.[38] This is thought to be a result of the desensitization of the capsaicin receptors as well as the onset of a hyperpolarizing response.[39]

CGRP is reportedly located in up to 50% of capsaicin-sensitive neurons, which range in size from small- to medium-sized cells.[40] These capsaicin-sensitive neurons not only act in a sensory role, but may also take part in the release of neurotransmitters involved in inflammation or edema associated with tissue injury.[41] In this instance, depolarization may cause both an action potential transmitted afferently and an efferent action generating the peripheral release of neuropeptides such as CGRP.[40,41]

Although a number of studies have examined the effects of capsaicin administration to limb joints,[42–50] none have investigated capsaicin's effects at the TMJ. This is important because of the possibility that the TMJ responds to insults in the same manner as limb joints. Furthermore, in these studies, the changes in neuropeptide levels over time have focused either on early time points (within 48 hours of administration) or relatively late time points (after 21 days). Thus, the purpose of our investigation was to determine if capsaicin application to the TMJ produces results similar to those observed in limb joint studies by altering levels of CGRP-like immunoreactivity (CGRP-ir) in the trigeminal ganglion at four specific time intervals: 4 hours, 48 hours, 10 days, and 21 days. These time periods were chosen both to examine results from acute (4 hours and 48 hours), intermediate (10 days), and chronic (21 days) time periods as well as to compare them with those obtained from other studies.

Materials and Methods

Surgical Procedures and Capsaicin Application

Twenty-six adult (200 to 250 g) female Sprague-Dawley rats were anesthetized with an intramuscular injection of Ketamine (Fort Dodge Laboratories, Fort Dodge, IA) and Rompun (Miles, Shawnee Mission, KS) (6.7:1) cocktail at a dosage of 1 mL/kg and maintained under deep anesthesia throughout the duration of the surgical procedure. The skin immediately superficial to the TMJ was shaved, and bilateral incisions were made at a point beginning posteroinferior to the lateral edge of the orbit and extending along the zygomatic arch to a point just rostral to the external ear canal. Subsequently, the musculature surrounding the TMJ was reflected by blunt dissection to expose the joint capsule. Capsaicin (Sigma, St Louis, MO), mixed with a vehicle containing 60% dimethylsulfoxide and 40% physiologic saline at a dose of 50 mg/kg as determined by Gamse et al[51] (10 mg capsaicin dissolved in 10 μL vehicle), was placed within the superior joint space of the left TMJ with a Hamilton (Reno, NV) microsyringe. An identical surgical procedure was employed on the right side, but vehicle only was placed, thus allowing each animal to serve as its own control. All incisions were sutured with 4-0 silk, and antibiotics were given prophylactically. Each animal was maintained under deep anesthesia for at least 1 hour after capsaicin application and subsequently monitored several times daily for signs of postsurgical trauma. After an initial weight loss for the first 2 to 3 days following surgery, the animals were at the normal weight for their age by the time of sacrifice (data not shown). Food and water were provided ad libitum, and all animals were maintained under normal light/dark cycles. All surgical procedures and sacrifice proto-

Table 1 CGRP Content (pg/mg Protein) in Trigeminal Ganglia at Various Time Intervals Following Injection†

Group	Time after injection			
	4 hours (n = 6)	48 hours (n = 8)	10 days (n = 6)	21 days (n = 6)
Vehicle-injected	5.89 ± 1.08	1.70 ± 0.56	6.68 ± 0.69	5.23 ± 1.23
Capsaicin-injected	2.00 ± 0.68*	3.40 ± 0.85**	4.68 ± 0.96*	9.89 ± 0.48**
Uninjected controls (n = 8)	5.12 ± 0.87			

†Data from untreated contol animals included for comparison.
*Different from vehicle-injected group at $P \leq 0.05$.
**Different from vehicle-injected group at $P \leq 0.01$.

cols were approved by the Baylor College of Dentistry Institutional Animal Care and Use Committee.

Animal Sacrifice and Tissue Preparation

After the surgeries, the injected animals were randomly divided into four groups and sacrificed at intervals of 4 hours, 48 hours, 10 days, and 21 days after capsaicin treatment. An additional eight animals were used as untreated controls. Each animal was anesthetized with an intraperitoneal injection of Nembutal (Abbott Laboratories, North Chicago, IL) (100 mg/kg) and transcardially perfused with 0.9% physiologic saline followed by 4% paraformaldehyde in 0.1 mol/L phosphate buffer, pH 7.4, to prepare the TMJs for histologic examination. Additionally, by means of the protocol first described by Gamse et al,[52] the trigeminal ganglia were bilaterally extirpated, homogenized in 0.5 mL of 2 mol/L acetic acid, and centrifuged. The resulting supernatant was saved, while the pellet was washed with 0.5 mL of 2 mol/L acetic acid and centrifuged. Next, the pellet was discarded and the two supernatants combined, lyophilized, and stored at –70°C until the radioimmunoassays (RIAs) were performed.

Radioimmunoassay for CGRP-ir

To normalize CGRP-ir content, a standard Folin Lowry protein assay was performed to assess total protein in the samples prior to running the RIAs.[53] Using the results from the Lowry assay, each tube in the assay received the same amount of protein to allow for comparisons between the CGRP-ir amounts obtained for each sample. Results were then expressed as pg CGRP-ir/mg total protein. Duplicate aliquots of the rehydrated supernatants were assayed using RIA kits (Research and Diagnostic Antibodies, Berkeley, CA) specific for CGRP-ir according to directions provided by the manufacturer.

Statistical Analysis

At each time interval, differences in CGRP-ir content between capsaicin and vehicle-injected sides were evaluated by means of Wilcoxon's signed rank test. However, because the RIAs for three of the time intervals were performed at a different time from the RIA of the second time interval, ratios were constructed so as to make each animal its own control, that is, CGRP-ir content on the capsaicin side was divided by CGRP-ir content on the vehicle side. These ratio data were compared to 1.0 (ratio indicating no difference between sides) by means of the Komolgorov-Smirnov test. Intra-assay and interassay coefficients of variability were 9% and 14%, respectively.

Results

The results of the RIA showed a pattern of cyclic changes in CGRP-ir content over time (Table 1). At 4 hours and at 10 days following capsaicin administration, CGRP-ir content was significantly

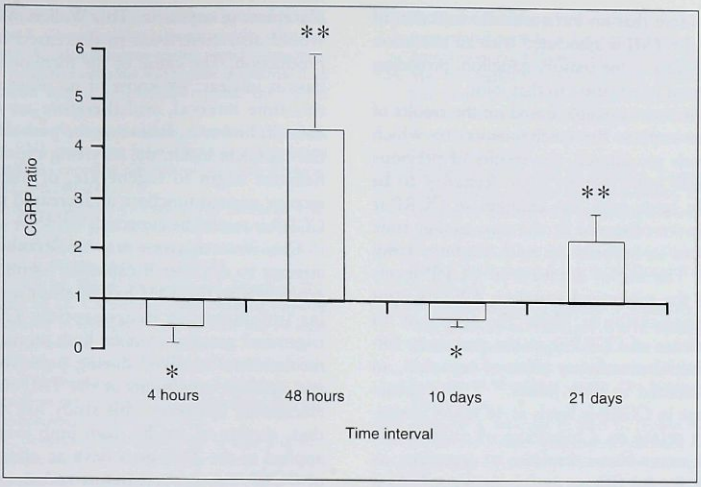

Fig 1 CGRP ratio (CGRP content of trigeminal ganglion on capsaicin-injected side divided by CGRP content on vehicle-injected side) for each time interval following injection. Data from untreated, control animals included also for comparison (*different from 1.0 at $P \leq 0.05$; **different from 1.0 at $P \leq 0.01$).

reduced on the capsaicin-injected side compared to the vehicle-injected side, whereas at 48 hours and at 21 days following capsaicin administration, CGRP-ir content was significantly elevated on the capsaicin-injected side. Analysis of the ratios of CGRP content on the capsaicin-injected versus the vehicle-injected side (Fig 1) graphically demonstrates the time course of the changes in neuropeptide content and their relative magnitude. At the 4-hour time interval, ganglia on the capsaicin-injected side experienced a roughly 50% decrease in CGRP-ir content in comparison to the vehicle-injected side, followed by a 400% increase at 48 hours. By 10 days, CGRP-ir content had once again dropped 30% below that in vehicle-injected animals. At the last time interval, 21 days, CGRP-ir content had become elevated by 200% on the capsaicin-injected side. Results from the untreated control animals demonstrated that there was no significant difference in comparison to the vehicle-injected side.

Discussion

CGRP has been shown to contribute to pain and inflammation both by its own vasodilatory actions and by its ability to modulate the actions of other neuropeptides. Numerous studies have investigated the role of CGRP in these conditions using limb joints as a model. However, while a few studies have examined this neuropeptide in the normal or inflamed TMJ, none have investigated the potential of capsaicin to affect neuropeptides acting at the TMJ.

The TMJ has been shown to be richly innervated by nerve fibers immunoreactive for CGRP. Studies in the rat reveal that nerve fibers containing CGRP-ir can be found within the joint capsule, articular disc, and synovial membrane, and appear to be highly localized adjacent to blood vessels.[54–56] In addition, clinical reports indicate that patients with arthritis at the TMJ have elevated levels of CGRP-ir in synovial joint fluid.[3–6] A particular contribution of this study

is to demonstrate that an intra-articular injection of capsaicin to the TMJ is associated with an alteration of CGRP-ir levels in the sensory ganglion, providing primary afferent innervation to that joint.

Although it is not possible based on the results of this study to explain the mechanism(s) by which CGRP-ir levels are altered, the results of previous studies in limb joints permit some scenarios to be proposed. In large part, the changes in CGRP-ir content that we observed at the two earlier time intervals were in accordance with findings from limb joints. The initial decrease in CGRP levels observed at the trigeminal ganglion 4 hours after capsaicin application is likely the result of an increased release of CGRP-ir at the periphery following the initial stimulatory effect of capsaicin, an effect documented in limb joints.[57,58] The subsequent increase in CGRP-ir levels at 48 hours postinjection may relate to a blockage of axoplasmic transport in nerve fibers sensitive to capsaicin, as has been shown by Gamse and coworkers.[59] As a result of this blockade, anterograde transport of the neuropeptides in capsaicin-sensitive neurons would presumably be inhibited. If so, CGRP-ir levels in the trigeminal ganglion would be expected to increase since the neuropeptide can no longer be transported away from those cell bodies of capsaicin-sensitive neurons involved in CGRP-ir production.

The factors underlying the changes at 10 and 21 days are less clear-cut, since most studies have been either truncated before this time or have used a considerably longer time interval. However, a possible explanation for the 10-day results may lie in the demonstrated importance of retrograde axonal transport of nerve growth factor (NGF) for the maintenance of CGRP-ir levels in sensory and sympathetic neurons involved in nociception.[60–65]

While the blockage of retrograde transport generally occurs during the first few days after capsaicin treatment, decreases in CGRP-ir content have been noted after this time. Lindsay and coworkers[63] showed that NGF-deprived dorsal root ganglion cells grown in culture exhibited a decrease in CGRP-ir levels after 1 to 2 days. Additionally, an in vivo study reported that CGRP-ir levels in dorsal root ganglia were below normal 7 days after the sciatic nerve was severed.[66] Accordingly, a blockage of axoplasmic transport that results in a short-term increase in CGRP-ir content might be expected to contribute to a decreased content in the longer term, owing to lack of NGF transport from the periphery. Jancso and colleagues,[67] Jancso and Ambrus,[68] and Jancso and Lawson[69] have further observed that many of the capsaicin-sensitive neurons begin to show signs of degeneration following perineural placement of capsaicin. This Wallerian-like response would also contribute to decreased neuropeptide production. The cause of the increased levels at 21 days is unclear; we know of no other studies using this time interval, and therefore no comparative data. If, however, following the pathology of an initial capsaicin insult, the surviving capsaicin-sensitive neurons begin to regenerate, or alternatively to recover normal function, an increased production of CGRP-ir would be expected.[30,33,66,70]

This investigation was undertaken as a first attempt to discover if capsaicin administered intra-articularly to the TMJ has an effect upon a particular inflammatory neuropeptide, CGRP, at the trigeminal ganglion. Unlike limb joints, many of the mechanisms involved during pain, inflammation, and arthritic conditions at the TMJ have yet to be elucidated. However, this study has demonstrated that, similar to results from limb joints, capsaicin applied to the TMJ does have an effect upon levels of CGRP. Further research is necessary to elucidate the mechanisms involved in the response of neurons in the trigeminal system to the application of capsaicin at the TMJ and what role, if any, this could play in treatment of TMD.

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References

1. Bush FM, Harkins SW, Harrington WG, Price DD. Analysis of gender effects on pain perception and symptom presentation in temporomandibular pain. Pain 1993;53:73–80.
2. Helkimo M. Epidemiological surveys of dysfunction of the masticatory system. In: Zarb GA, Carlsson GE (eds). Temporomandibular Joint—Function and Dysfunction. Copenhagen: Munksgaard, 1979:175–192.
3. Alstergren P, Appelgren A, Appelgren B, Kopp S, Lundeberg T, Theodorsson E. Co-variation of neuropeptide Y, calcitonin gene-related peptide, substance P and neurokinin A in joint fluid from patients with temporomandibular joint arthritis. Arch Oral Biol 1995;40:127–135.
4. Appelgren A, Appelgren B, Eriksson S, Kopp S, Lundeberg T, Nylander M, et al. Neuropeptides in temporomandibular joints with rheumatoid arthritis: A clinical study. J Dent Res 1991;99:519–521.
5. Appelgren A, Appelgren B, Kopp S, Lundeberg T, Theodorsson E. Relation between intra-articular temperature of the arthritic temporomandibular joint and presence of calcitonin gene-related peptide in the joint fluid. Acta Odontol Scand 1993;51:285–291.

6. Holmlund A, Ekblom A, Hansson P, Lind J, Lundeberg T, Theodorsson E. Concentrations of neuropeptides substance P, neurokinin A, calcitonin gene-related peptide, neuropeptide Y and vasoactive intestinal polypeptide in synovial fluid of the human temporomandibular joint. Int J Oral Maxillofac Surg 1991;20:228–231.
7. Amara SG, Jonas V, Rosenfeld MG, Ong ES, Evans RM. Alternative RNA processing in calcitonin gene expression generates mRNAs encoding different polypeptide products. Nature 1982;298:240–244.
8. Rosenfeld MG, Mermod J, Amara SG, Swanson LW, Sawchenko PE, Rivier J, et al. Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing. Nature 1983;304:129–135.
9. Gibson SJ, Polak M, Bloom SR, Sabate IM, Mulderry PM, Ghatei MA, et al. Calcitonin gene-related peptide immunoreactivity in the spinal cord of man and of eight other species. J Neurosci 1984;4:3101–3111.
10. Kawai Y, Takami K, Shiosaka S, Emson PC, Hillyard CJ, Girgis S, et al. Topographic localization of calcitonin gene-related peptide in the rat brain: An immunohistochemical analysis. Neuroscience 1985;15:747–763.
11. McNeil DL, Coggeshall RE, Carlton SE. A light and electron microscopic study of calcitonin gene-related peptide in the spinal cord of the rat. Expl Neurol 1988;99:699–708.
12. Skofitsch G, Jacobowitz DM. Calcitonin gene-related peptide: Detailed immunohisto-chemical distribution in the central nervous system. Peptides 1985;6:721–745.
13. Franco-Cereceda A, Henke H, Lundberg JM, Peterman JB, Hokfelt T, Fisher JA. Calcitonin gene-related peptide (CGRP) in capsaicin sensitive substance P-immunoreactive sensory neurons in animals and man. Distribution and release by capsaicin. Peptides 1987;8:399–410.
14. Hokfelt T, Arvidsson U, Ceccateli S, Cortes R, Cullheim S, Dagerlind A, et al. Calcitonin gene-related peptide in the brain, spinal cord, and some peripheral systems. Ann NY Acad Sci 1992;657:119-134.
15. Ishida-Yamamoto A, Tohyama M. Calcitonin gene-related peptide in the nervous tissue. Prog Neurobiol 1989;33: 335–386.
16. Kashihara Y, Sakaguchi M, Kuno M. Axonal transport and distribution of endogenous calcitonin gene-related peptide in rat peripheral nerve. J Neurosci 1989;11:3796–3802.
17. Skofitsch G, Jacobowitz DM. Calcitonin gene-related peptide coexists with substance P in capsaicin sensitive neurons and sensory ganglia of the rat. Peptides 1985;6:747–754.
18. Zaidi M, Moonga BS, Bevis PJR, Bascal ZA, Breimer LH. The calcitonin gene peptides: Biology and clinical relevance. Crit Rev Clin Lab Sci 1990;28:109–174.
19. Lee Y, Kawai Y, Shiosaka S, Takami K, Kiyama H, Hillyard CJ, et al. Coexistence of calcitonin gene-related peptide and substance P-like peptide in single cells of the trigeminal ganglion of the rat: Immunohistochemical analysis. Brain Res 1985; 330:194–196.
20. Lee Y, Takami K, Kawai Y, Hillyard CJ, MacIntyre I, Emson PC, et al. Distribution of calcitonin gene-related peptide in the rat peripheral nervous system with reference to its coexistence with substance P. Neuroscience 1985;15: 1227–1237.
21. Brain SD, Williams TJ, Tippins JR, Morris HR, MacIntyre I. Calcitonin gene-related peptide is a potent vasodilator. Nature 1985;313:54–56.
22. Cambridge H, Brain SD. Calcitonin gene-related peptide increases blood flow and potentiates plasma protein extravasation in the rat knee joint. Br J Pharmacol 1992; 106:746–750.
23. Le Greves P, Nyberg F, Terenius L, Hokfelt T. Calcitonin gene-related peptide is a potent inhibitor of substance P degradation. Eur J Pharm 1985;115:309–311.
24. Mao J, Coghill RC, Kellstein DE, Frenk H, Mayer DJ. Calcitonin gene-related peptide enhances substance P-induced behaviours via metabolic inhibition: In vivo evidence for a new mechanism of neuromodulation. Brain Res 1992;574:157–163.
25. Oku R, Satoh M, Fujii M, Otaka A, Yajima H, Takagi H. Calcitonin gene-related peptide promotes mechanical nociception by potentiating release of substance P from the spinal dorsal horn in rats. Brain Res 1987;403:350–354.
26. Wallengren J, Wang Z. Interaction between tachykinins and CGRP in human skin. Acta Derm Venereol 1993; 73:259-261.
27. Wiesenfeld-Hallin Z, Hokfelt T, Lundberg JM, Forsmann WG, Reinecke M, Tschopp FA, et al. Immunoreactive calcitonin gene-related peptide and substance P coexist in sensory neurones to the spinal cord and interact in spinal behavioral responses of the rat. Neurosci Lett 1984; 52:199–204.
28. Donnerer J, Schuligoi R, Stein C, Amann R. Upregulation, release and axonal transport of substance P and calcitonin gene-related peptide in adjuvant inflammation and regulatory function of nerve growth factor. Regul Pept 1993; 46:150–154.
29. Hanesch U, Pfrommer U, Grubb BD, Schaible H. Acute and chronic phases of unilateral inflammation in rats' ankles are associated with an increase in the proportion of calcitonin gene-related peptide-immunoreactive dorsal root ganglion cells. Eur J Neurosci 1993;5:154–161.
30. Kuraishi Y, Nanayama T, Ohno H, Fujii M, Otaka A, Yajima H, et al. Calcitonin gene-related peptide increases in the dorsal root ganglia of adjuvant arthritic rat. Peptides 1989;10:447–452.
31. Nahin RL, Byers MR. Adjuvant-induced inflammation of rat paw is associated with altered calcitonin gene-related peptide immunoreactivity within cell bodies and peripheral endings of primary afferent neurons. J Comp Neurol 1994;349:475–485.
32. Smith GD, Harmar AJ, McQueen DS, Seck JR. Increases in substance P and CGRP, but not somatostatin content of innervating dorsal root ganglia in adjuvant monoarthritis in the rat. Neurosci Lett 1992;137:257–260.
33. Galeazza MT, Garry MG, Yost HJ, Strait KA, Hargreaves KM, Seybold VS. Plasticity in the synthesis and storage of substance P and calcitonin gene-related peptide in primary afferent neurons during peripheral inflammation. Neurosci 1995;66:443–458.
34. Sluka KA, Dougherty PM, Sorkin LS, Willis WD, Westlund KN. Neural changes in acute arthritis in monkeys. III. Changes in substance P, calcitonin gene-related peptide and glutamate in the dorsal horn of the spinal cord. Brain Res Rev 1992;17:29–38.
35. Buck SH, Burks TF. The neuropharmacology of capsaicin: Review of some recent observations. Pharmacol Rev 1986; 38:179–226.
36. Szolcsanyi J, Jancso-Gabor A. Sensory effects of capsaicin congeners. I. Relationship between chemical structure and pain-producing potency of pungent agents. Drug Res 1975;25:1877–1881.
37. Szolcsanyi J, Jancso-Gabor A. Sensory effects of capsaicin congeners. II. Importance of chemical structure and pungency in desensitizing activity of capsaicin-type compounds. Drug Res 1976;26:33–37.

38. Szolcsanyi J. Capsaicin type pungent actions producing pyrexia. In: Milton AS (ed). Pyretics and Antipyretics. Handbook of Experimental Pharmacology, vol 60. Berlin: Springer, 1982:437–478.
39. Bevan SJ, Docherty RJ. Cellular mechanisms of the action of capsaicin. In: Wood JN (ed). Capsaicin in the Study of Pain. London: Academic Press, 1993:27–44.
40. Holzer P. Capsaicin: Cellular targets, mechanisms of action and selectivity for thin sensory neurons. Pharmacol Rev 1991;43:143–201.
41. Maggi CA. The pharmacological modulation of neurotransmitter release. In: Wood JN (ed). Capsaicin in the Study of Pain. London: Academic Press, 1993:161–190.
42. Ahmed M, Bjurholm A, Srinivasan GR, Lundeberg T, Theodorsson E, Schultzberg M, et al. Capsaicin effects on substance P and CGRP in rat adjuvant arthritis. Regul Pept 1995;55:85–102.
43. Colpaert FC, Donnerer J, Lembeck F. Effects of capsaicin on inflammation and on the substance P content of nervous tissues in rats with adjuvant arthritis. Life Sci 1983;32:1827–1834.
44. Ferrell WR, Lam FY, Montgomery I. Differences in the axon composition of nerves supplying the rat knee joint following intra-articular injection of capsaicin. Neurosci Lett 1992;141:259–261.
45. He X, Schepelmann K, Schaible HG, Schmidt RF. Capsaicin inhibits responses of fine afferents from the knee joint of the cat to mechanical and chemical stimuli. Brain Res 1990;530:147–150.
46. He X, Schmidt RF, Schmittner H. Effects of capsaicin on articular afferents of the cat's knee joint. Agents Actions 1988;25:222–224.
47. Inman RD, Chiu B, Rabinovich S, Marshall W. Neuromodulation of synovitis: Capsaicin effect on severity of experimental arthritis. J Neuroimmunol 1989;24:17–22.
48. Lam FY, Ferrell WR. Capsaicin suppresses substance P-induced joint inflammation in the rat. Neurosci Lett 1989;105:155–158.
49. Lam FY, Ferrell WR. Specific neurokinin receptors mediate plasma extravasation in the rat knee joint. Br J Pharmacol 1991;103:1263–1267.
50. Marinozzi G, Ferrante F, Gaudio E, Ricci A, Amenta F. Intrinsic innervation of the rat knee joint articular capsule and ligaments. Acta Anat 1991;141:8–14.
51. Gamse R, Leeman SE, Holzer P, Lembeck F. Differential effects of capsaicin on the content of somatostatin, substance P, and neurotensin in the nervous system of the rat. Arch Pharmacol 1981;317:140–148.
52. Gamse R, Lembeck F, Cuello AC. Substance P in the vagus nerve: Immunochemical and immunohistochemical evidence for axoplasmic transport. Naunyn Schmiedebergs Arch Pharmacol 1979;306:37–44.
53. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. J Biol Chem 1951;193:265–275.
54. Ichikawa H, Matsuo S, Wakisaka S, Akai M. Fine structure of calcitonin gene-related peptide-immunoreactive nerve fibers in the rat temporomandibular joint. Arch Oral Biol 1990;35:727–730.
55. Ichikawa H, Wakisaka S, Matsuo S, Akai M. Peptidergic innervation of the temporomandibular disk in the rat. Experientia 1989;45:303–304.
56. Kido MA, Kiyoshima T, Kondo T, Ayasaka N, Moroi R, Terada Y, et al. Distribution of substance P and calcitonin gene-related peptide-like immunoreactive nerve fibers in the rat temporomandibular joint. J Dent Res 1993; 72:592–598.
57. Holzer P. Local effector function of capsaicin-sensitive sensory nerve endings: Involvement of tachykinins, calcitonin gene-related peptide, and other neuropeptides. Neuroscience 1988;24:739–768.
58. Maggi CA, Meli A. The sensory-efferent function of capsaicin-sensitive nerves. Gen Pharmacol 1988;19:1–43.
59. Gamse R, Petsche U, Lembeck F, Jancso G. Capsaicin applied to peripheral nerve inhibits axoplasmic transport of substance P and somatostatin. Brain Res 1982; 239:447–462.
60. Donnerer J, Schuligoi R, Stein C. Increased content and transport of substance P and calcitonin gene-related peptide in sensory nerves innervating inflamed tissue: Evidence for a regulatory function of nerve growth factor in vivo. Neuroscience 1992;49:693–698.
61. Goedert M, Stoeckel K, Otten U. Biological importance of the retrograde axonal transport of nerve growth factor in sensory neurons. Proc Natl Acad Sci USA 1981; 78:5895–5898.
62. Lindsay RM, Harmar AJ. Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons. Nature 1989;337:362–364.
63. Lindsay RM, Lockett C, Sternberg J, Winter J. Neuropeptide expression in culture of adult sensory neurons: Modulation of substance P and calcitonin gene-related peptide levels by nerve growth factor. Neuroscience 1989;33:53–65.
64. Wong J, Oblinger MM. NGF rescues substance P expression but not neurofilament or tubulin gene expression in axotomized sensory neurons. J Neurosci 1991;11: 543–552.
65. Yip HK, Rich KM, Lamoe PA, Johnson EM. The effects of nerve growth factor and antiserum on the post-natal development and survival after injury of sensory neurons in the rat dorsal root ganglia. J Neurosci 1984;4: 2986–2992.
66. Inaishi Y, Kashihara Y, Sakaguchi M, Kuno M. Co-operative regulation of calcitonin gene-related peptide levels in rat sensory neurons via their central and peripheral processes. J Neurosci 1992;12:518–524.
67. Jancso G, Kiraly E, Joo F, Such G, Nagy A. Selective degeneration by capsaicin of a subpopulation of primary sensory neurons in the adult rat. Neurosci Lett 1985; 59:209–214.
68. Jancso G, Ambrus A. Capsaicin sensitivity of primary sensory neurones and its regulation. In: Besson JM, Guibaud G, Ollat H (eds). Peripheral Neurons in Nociception: Physio-Pharmacological Aspects. Paris: John Libbey Eurotext, 1994:71–87.
69. Jancso G, Lawson SN. Transganglionic degeneration of capsaicin-sensitive C-fiber primary afferent terminals. Neuroscience 1990;39(2):501–511.
70. Winter F, Woolf C, Lynn B. Degenerative and regenerative responses of sensory neurons to capsaicin-induced damage. In: Wood JN (ed). Capsaicin in the Study of Pain. London: Academic Press, 1993:139–160.

Resumen

La aplicación de capsaicina a la articulación temporomandibular altera los niveles del péptido relacionado al gen de la calcitonina en el ganglio trigémino de la rata

El propósito de esta investigación fue el de determinar el efecto temporal de una inyección intra-articular de capsaicina a la articulación temporomandibular, sobre los niveles de inmunoreactividad del péptido relacionado al gen de la calcitonina (ir-PRGC) en el ganglio trigémino de la rata. Se inyectaron las articulaciones de 26 ratas hembras adultas en un lado con capsaicina y contralateralmente con un vehículo de control. Ocho animales adicionales sirvieron de control, y no recibieron inyecciones. Los animales fueron sacrificados de acuerdo a intervalos de tiempo de 4 horas, 48 horas, 10 días, y 21 días luego del tratamiento. Se extirparon los ganglios trigéminos, y los niveles de ir-PRGC fueron cuantificados por medio de un radioinmunoensayo. Al comparar los resultados del lado que fue tratado con la capsaicina y el lado tratado con el vehículo, los niveles de ir-PRGC disminuyeron inicialmente a las 4 horas y aumentaron a las 48 horas. A los 10 días, los niveles de ir-PRGC habían disminuido de nuevo, bajo los niveles de control, seguidos por un aumento a los 21 días. Los niveles de ir-PRGC durante los primeros dos períodos de tiempo investigados, que simulan un estado inflamatorio agudo, imitan los resultados observados en estudios utilizando articulaciones de miembros; mientras que los otros períodos de tiempo, que representan una condición crónica e intermedia, respectivamente, indican una interacción más compleja con los aferentes primarios sensibles a la capsaicina.

Zusammenfassung

Capsaicin Applikation an das Kiefergelenk verändert den Calcitonin Gen- bezogenen Peptid Spiegel in dem Ganglion semilunare der Ratte

Zweck dieser Unersuchung war es, den temporalen Effekt der intraaurikularen Injektion von Capsaicin in das Kiefergelenk auf die Gen-bezogene Peptid-änliche immunore-aaktivität (CORP-ir) zu untersuchen. Kiefergelenke von 28 weibliche Ratten wurden einsetig mit Capsaicin injiziert, die kontralaterale Seite wurde mit Kontrollflüssigkeit behandelt. Acht Ratten dienten als Kontrolltiere ind blieben unbehandelt. Tiere wrden nach 4 Stunden, 48 Stunden, 10 Tage und 21 Tage getötet. Die Ganglia semilunare wurden durch Radioimmunoanalyse untersucht. Vergleich der Ergebnisse zwichen der mit Capsaicin behandelte Seite und der anderen Seite zeigte, dass der CORP-ir Spiegel nach 4 Stunden abnahm, um nach 48 Stunden zu steigen. Nach 10 Tage war der CORP-ir Spiegel wieder unter den Ausgangswerte, um nach 21 Tage wieder zu steigen. CORP-ir Spiegel für die beiden ersten Intervalle, die einen akuten Entzündungsstatus simulieren, scheinen Studien mit Gliedgelenke nachzuahmen. Die beiden andere Zeitintervalle, die intermediäre, bzw. chronische Entzündungsstadien entsprechen, lassen auf ein komplexeres Zusammenspiel mit afferent Capsaicin-empfindliche Faser schliessen.