A Model for the Study of Experimentally Induced Temporomandibular Arthritis in Rats: The Effect of Human Recombinant Interleukin-1α on Neuropeptide-like Immunoreactivity

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To study the interaction between human recombinant interleukin-1α and the nervous system, substance P–, neurokinin A–, calcitonin gene–related peptide–, and neuropeptide Y–like immunoreactivity in the cerebrospinal fluid, plasma, and temporomandibular joint (TMJ) perfusates of rats during acute experimental monarthritis were examined. The right TMJs of the experimental rats were injected with 0.01 mL of human recombinant interleukin-1α. The right TMJs of control rats were injected with 0.01 mL of saline. Cerebrospinal fluid, plasma, and perfusates from the right TMJs were obtained at 2, 6, and 24 hours following injection, and neuropeptide-like immunoreactivity was analyzed by specific radioimmunoassays. Values of neuropeptide-like immunoreactivity for the experimental rats were compared with those of the control rats. In the experimental group, substance P–, neurokinin A–, and calcitonin gene–related peptide–like immunoreactivities were increased in cerebrospinal fluid compared to those of the control group. In plasma, no changes in neuropeptide-like immunoreactivities were generally seen. Substance P–, neurokinin A–, calcitonin gene–related peptide–, and neuropeptide Y–like immunoreactivities rose significantly in the TMJ perfusates. Most pronounced changes in neuropeptide Y–like immunoreactivity occurred intra-articularly in the TMJ perfusates. The results indicate that the contribution of the nervous system to human recombinant interleukin-1α–induced monarthritis is most pronounced in the affected joint.

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Interleukin-1 (IL-1) is one of the most important mediators of host defensive reactions. Among the functions attributed to IL-1 are the induction of fever, acute-phase protein synthesis, prostaglandin production, and immune system activation.[1] It has been demonstrated that intraperitoneal administration of IL-1 activates the pituitary-adrenal axis through a release of corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH).[2,3] On the other hand, immune system activity is inhibited by glucocorticoids,[4–6] indicating the existence of a negative feedback loop between the immune system and the pituitary-adrenal axis.

Recently the neuroimmunomodulatory role of different neuropeptides found in afferent nerve fibers has attracted much interest. It has been reported that substance P (SP)[7,8] and neurokinin A (NKA)[9] can activate immunologic mechanisms; calcitonin gene-related peptide (CGRP)[9–11] has a modulatory effect on the immune system. Both SP and NKA have been shown to release IL-1 from human blood monocytes[12] and to enhance IL-1-like activity in a mouse macrophage cell line P388D1.[13] Furthermore, IL-1 has been shown to increase SP gene expression[14] and SP levels in sympathetic ganglia.[15] Apart from effects on the immune system, SP,[16] NKA,[17] and CGRP[18] have been shown to induce plasma extravasation and vasodilatation and thus might be important mediators of neurogenic inflammation. Both SP and CGRP have been shown to be colocalized in afferent nerves[19] and simultaneously released from the rat spinal cord.[20]

A neuropeptide that is released from postganglionic sympathetic nerve efferents is neuropeptide Y (NPY). It has been shown that NPY can modulate SP release from rat sensory neurons,[21] perhaps because of its vasoconstrictive effect.[22] Recently, it was found that unilateral intra-articular injection of proinflammatory substances induces a bilateral increase in SP-, NKA-, CGRP-, and NPY-like immunoreactivity (-LI) in rat synovial fluid,[23] as well as an increase in the concentrations of SP-LI in the cerebrospinal fluid during acute monarthritis.[24]

The aim of the present study was to investigate the interaction between the immune and nervous systems by measuring changes in SP-, NKA-, CGRP-, and NPY-LI in rat cerebrospinal fluid, plasma, and perfusates of the right temporomandibular joints (TMJs) at 2, 16, and 24 hours after intra-articular injection of IL-1.

Materials and Methods

The study was carried out on 50 male albino Sprague-Dawley rats weighing 250 to 300 g. On the day of the experiment, the rats were anesthetized with chloral hydrate (0.4 g/kg). The skin overlying the TMJs was shaved before the intra-articular injections. Thirty rats were injected with 0.01 mL of human recombinant interleukin-1α (hrIL-1α) (1 mg/mL) via a 27-gauge needle into the right TMJ. The right-side TMJs of 20 control rats were injected with 0.01 mL of saline. After periods of 2, 6, and 24 hours following injection, the rats were again anesthetized with chloral hydrate. A 1-cm longitudinal skin incision was made, exposing the TMJs, and a 27-gauge needle was inserted. The joints were perfused with 0.15 mL of 0.9% saline through the 27-gauge needle using a push-and-pull technique. Collection of perfusates was carried out for 15 minutes and resulted in a 0.1-mL perfusate.

For collection of cerebrospinal fluid, rats were placed in a stereotactic frame. The atlanto-occipital membrane was exposed by retracting the overlying muscles. Samples of 80 to 150 μL of cerebrospinal fluid were obtained through a 27-gauge needle connected to a 1-mL syringe via polyethylene tubing.

Blood (1.5 to 4.5 mL) was collected by a puncture of the heart with a vacutainer tube containing 143 IU of heparin. Afterward, 500 IU/mL of aprotinin (Trasylol, Bayer, Leverkusen, Germany) was added. The samples were centrifuged, and plasma was removed and frozen. All samples were rapidly cooled and stored at −80°C until analysis. Samples from the cerebrospinal fluid, plasma, and perfusates were extracted using a reverse-phase C18 cartridge (Sep Pak, Waters, Milford, MA) and analyzed using competitive radioimmunoassays.[25,26] Radioimmunoassays of SP-, CGRP-, NKA-, and NPY-LI were done using antiserums SP2, CGRPR8, K12, and N1, respectively. The lower detection limit in all extracts was 0.1 fmol/mL for all peptides assessed. The mean and one standard deviation were used as measures of central tendency and variation. Mann-Whitney nonparametric analysis of variance was used to test for differences between two groups. Spearman's rank correlation coefficient was used to analyze the correlation between groups ($P < .05$).

Results

Cerebrospinal Fluid

The SP-LI was increased in cerebrospinal fluid of experimental rats compared to control rats at 6 hours and 24 hours following intra-articular injection of hrIL-1α. The NKA-LI and CGRP-LI of the experimental rats were increased compared with that of the control rats. The NPY-LI was not increased in experimental rats compared to control rats following injection of hrIL-1α (Table 1).

Plasma

No statistically significant changes in SP-, CGRP-, or NPY-LI were seen in plasma following injection of hrIL-1α. The NKA-LI of the experimental rats

was significantly reduced in comparison to that of the control rats (Table 2).

Temporomandibular Perfusates

There was generally an increase in neuropeptide-LI in the perfusates from the TMJs following injection of hrIL-1α (Table 3).

Discussion

Interleukin-1 is known to exist in two molecular forms, IL-1α and IL-1ß. Interleukin-1α may be functionally active in its cell-associated form as well as in its secreted form. However, IL-1ß is effective only in the secreted form.[27] The presence of circulating IL-1–containing cells[28] and enhanced levels of plasma containing IL-1ß have been seen in the plasma of rheumatoid arthritis patients[29] and are correlated with disease activity. Interleukin-1 activity has been demonstrated in synovial fluid from patients with different rheumatic and inflammatory conditions,[30] and IL-1 production is elevated in macrophages from adjuvant-induced rats.[31] The presence of IL-1 in joints seems to be of synovial cell origin[32] including dendritic cells, macrophages, and synovial fibroblasts. It has been shown that IL-1 can regulate its own production by inducing gene expression of IL-1α and IL-1ß in synovial fibroblasts and peripheral blood monocytes,[33] thereby promoting the inflammatory process.

In the present study, an intra-articular injection of hrIL-1α increased neuropeptide-LI mainly in the perfusates from the TMJ, with the exception of SP-LI, which was elevated only at 2 hours following injection. It is known that SP, NKA, and CGRP participate in neurogenic inflammation, and bilaterally increased concentrations of these neuropeptide-LI have been shown in the perfusates from knee joints following unilateral injection of either Freund adjuvant or carrageenan.[23,24] Interleukin-1 can directly increase SP content in cultured sympathetic ganglia.[15] It has also been reported that endopeptidase 24.11 (enkephalinase), which is responsible for SP and NKA metabolism,[34] inactivates IL-1.[35]

Our findings concerning SP-LI in perfusates following hrIL-1α are in line with results of O'Byrne et al,[36] who used lower doses (59 mg) than those used in the present study. In their study, an intra-articular injection of hrIL-1α (100 ng) into the rabbit knee enhanced SP-LI at 4, 24, and 48 hours in the joint lavage fluid; no SP-LI was found fol-

Table 1 Concentrations (fmol/mL) in Cerebrospinal Fluid at 2, 6, and 24 Hours After Treatment of Saline in Control TMJs and hrIL-1α in Experimental TMJs

	2 h	6 h	24 h
Saline			
SP-LI	< 0.1	< 0.1	< 0.1
NKA-LI	< 0.1	< 0.1	< 0.1
CGRP-LI	28.2 ± 4.6	29.5 ± 6.1	24.7 ± 2.9
NPY-LI	1411 ± 311	1243 ± 314.2	2921 ± 624.2
hrIL-1α			
SP-LI	< 0.1	36.2 ± 22.4*	45.3 ± 19.8*
NKA-LI	14.2 ± 6.3**	68.1 ± 30.2**	112 ± 48.4**
CGRP-LI	42.4 ± 10.3*	45.6 ± 12.4*	48.4 ± 18.6*
NPY-LI	1232 ± 246	1148 ± 198	1873 ± 256

Statistically significant differences from saline-treated control rats:
*$P < .05$.
**$P < .01$.

Table 2 Concentrations (fmol/mL) in Plasma at 2, 6, and 24 Hours After Treatment of Saline in Control TMJs and hrIL-1α in Experimental TMJs

	2 h	6 h	24 h
Saline			
SP-LI	0.4 ± 0.4	0.4 ± 0.2	1.1 ± 0.7
NKA-LI	7.3 ± 2.2	6.4 ± 3.1	7.5 ± 2.4
CGRP-LI	5.2 ± 1.1	3.9 ± 0.7	3.8 ± 1.1
NPY-LI	485.2 ± 182.3	522.3 ± 262.9	568.1 ± 263.2
hrIL-1α			
SP-LI	0.6 ± 0.5	1.9 ± 1.6	2.6 ± 3.1
NKA-LI	< .01***	< 0.1***	< 0.1***
CGRP-LI	12.2 ± 6.4	8.4 ± 4.7	8.9 ± 6.8
NPY-LI	473.6 ± 212.2	679.4 ± 398.1	439.3 ± 314.2

Statistically significant differences from saline-treated control rats:
*$P < .05$.
**$P < .01$.

Table 3 Concentrations (fmol/mL) in TMJ Perfusate at 2, 6, and 24 Hours After Treatment of Saline in Control TMJs and hrIL-1α in Experimental TMJs

	2 h	6 h	24 h
Saline			
SP-LI	< 0.1	< 0.1	< 0.1
NKA-LI	< 0.1	< 0.1	< 0.1
CGRP-LI	2.2 ± 1.5	2.7 ± 1.1	2.6 ± 0.9
NPY-LI	193 ± 6.4	17.2 ± 7.3	19.6 ± 5.8
hrIL-1α			
SP-LI	2.2 ± 1.4**	< 0.1	< 0.1
NKA-LI	5.2 ± 2.3**	5.1 ± 3.4*	4.2 ± 2.2**
CGRP-LI	6.9 ± 1.1*	6.2 ± 0.2**	6.6 ± 0.1**
NPY-LI	69.8 ± 0.4***	46.2 ± 4.4**	44.8 ± 8.1**

Statistically significant differences from saline-treated control rats:
*$P < .05$.
**$P < .01$.

lowing an intra-articular injection of 1 mg. We could detect increased levels of SP-LI at only 2 hours following injection, despite the much higher doses of hrIL-1α used. However, different doses of IL-1α may result in different mechanisms of action, and species differences may influenced the outcomes as well.

In a recent study,[37] injection of carrageenan into the left plantar hind paw of the rat resulted in an ipsilateral increase in paw volume, which was paralleled by an increased content of CGRP-like immunoreactivity in both ipsilateral and contralateral paw perfusates. Previous studies have demonstrated increased biosynthesis of CGRP in the dorsal root ganglia[13] and increased release of CGRP-like immunoreactivity in the spinal cord[38] in response to experimentally induced inflammation. Furthermore, it has been reported that experimentally induced monarthritis results in changes of vascular reactivity[39,40] and an increase in the number of infiltrating cells[41,42] in the opposite joint. It is also suggested that the bradykinin-induced plasma extravasation observed in both the injected and contralateral knee joints[43] may be influenced by a neurogenic mechanism.[44] However, in the present study, no contralateral joint swelling was clinically apparent. Taken together, the results indicate that there is a link whereby increased activity in sensory and sympathetic neurons contributes to TMJ arthritis. Also, SP and NKA have been shown to induce the release of IL-1 from human monocytes at 6 hours[12] and to enhance IL-1 activity in mouse macrophage cell line P388D1.[13] Coderre et al[45] demonstrated the role of the sympathetic nervous system in experimentally induced arthritis. However, in the present study, NPY-LI was elevated mainly in the TMJ perfusates. Such local increases might indicate a possible role for NPY and the other neuropeptides in the TMJ during inflammation.[46–50]

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Resumen

Un Modelo para el Estudio de la Artritis Inducida Experimentalmente en Ratas: El efecto de la Interleucina-1α sobre la Inmunoreactividad de Tipo Neuropéptido

Se examinaron los líquidos de perfusión en ratas durante una situación de monartritis experimental aguda, para estudiar la interacción entre la interleucina-1α recombinante humana y el sistema nervioso, la sustancia P, la neurocinina A, el péptido relacionado al gen de la calcitonina, y la inmunoreactividad tipo neuropéptido en el fluido cerebroespinal, el plasma y la articulación temporomandibular (ATM). Las ATM derechas de las ratas experimentales fueron inyectadas con 0,01 mL de interleucina-1α recombinante humana. Las ATM derechas de las ratas de control fueron inyectadas con 0,01 mL de solución salina. El fluido cerebroespinal, el plasma, y los líquidos de perfusión de las ATM derechas fueron obtenidos a las 2, 6 y 24 horas luego de la inyección, y la inmunoreactividad tipo neuropéptido fue analizada por radioinmunoensayos específicos. Los valores de la inmunoreactividad tipo neuropéptido de las ratas experimentales fueron comparados a aquellos de las ratas de control. En el grupo experimental la inmunoreactividad de la sustancia P-, la neurocinina A-, y la del tipo péptido relacionada al gen de la calcitonina, estaba aumentada en el fluido cerebroespinal en comparación con aquella del grupo de control. En el plasma, en general no se vieron cambios en la inmunoreactividad de tipo neuropéptido. La sustancia P-, la neurocinina A -, el péptido relacionado al gen de la calcitonina y la inmunoreactividad de tipo neuropéptido Y, aumentaron significativamente en los líquidos de perfusión de la ATM. Los cambios mas pronunciados en la inmunoreactividad tipo neuropéptido Y ocurrieron intra-articularmente en los Líquidos de la ATM. Los resultados indican que la contribución del sistema nervioso a la monartritis inducida por la interleucina-1α recombinante humana, está posiblemente limitada a la articulación afectada.

Zusammenfassung

Ein Modell für die Studie von experimentell induzierter Kiefergelenksarthritis bei Ratten: Der Effekt von menschlichem rekombinantem Interleukin-1α auf die neuropeptidartige Immunreaktivität

Um die Wechselwirkung zwischen menschlichem rekombinantem Interleukin-1α und dem Nervensystem zu untersuchen, wurden bei Ratten die Immunreaktivität folgender Substanzen im Liquor, Plasma und im Kiefergelenk während einer akuten experimentellen Monarthritis gemessen: Substance P, Neurokinin A, Calcitonin gene-related Peptide und Neuropeptide Y. In das rechte Kiefergelenk der Versuchsratten wurde 0.01 mL humanes rekombinantes Interleukin-1α injiziert. In das rechte Kiefergelenk von Kontrollratten wurde 0.01 mL Kochsalzlösung injiziert. Nach 2, 6 und 24 Stunden wurden Proben von Liquor, Plasma und der Kiefergelenksflüssigkeit gewonnen und die neuropeptidartige Immunreaktivität mit spezifischen Radioimmuntests analysiert. Bei der Versuchsgruppe waren die Immunreaktivitätswerte von Substance P, Neurokinin A und Calcitonin gene-related peptide im Liquor im Vergleich zu der Kontrollgruppe erhöht. Im Plasma waren keine Unterschiede zu erkennen. Bei den Kiefergelenken waren sämtliche Werte signifikant erhöht. Die Resultate legen nahe, dass der Beitrag des Nervensystems zu Interleukin-1α-induzierter Monarthritis möglicherweise auf das betroffene Gelenk beschränkt ist.