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Pain is an inherent component of inflammation often accompanying immune response. A large spectrum of molecules released within the inflamed tissue induces pain by stimulating primary afferent neurons in situ. Activity of primary sensitive fibers can be counteracted by local opioid release by leukocytes. In this study, we investigated the endogenous regulation of CFA-induced inflammatory pain in the context of adaptive T cell immune response. The nociceptive response to mechanical stimuli was studied using von Frey filaments in mice immunized with OVA in CFA. The nociceptive response of nude versus wild-type mice was dramatically increased, demonstrating T cell deficiency associated with increased pain sensitivity. Based on adoptive transfer experiments of OVA-specific CD4+ T lymphocytes into nude mice, we show that Ag-specific activated, but not resting T lymphocytes are responsible for the spontaneous relief of inflammation-induced pain following Ag challenge. The analgesia was dependent on opioid release by Ag-primed CD4+ T lymphocytes at the inflammatory site. Indeed, T cell-mediated analgesia was inhibited by local injection of an opioid receptor antagonist, unable to cross the blood-brain barrier. Notably, we found opioid precursor mRNA to be >7-fold increased in Ag-specific activated CD4+ T lymphocytes, as compared with resting T lymphocytes in vivo. Taken together, our results show that CD4+ T lymphocytes acquire antinociceptive effector properties when specifically primed by Ag and point out analgesia as a property linked to the effector phase of adaptive T cell response. The Journal of Immunology, 2011, 186: 5078–5084.

Materials and Methods
Adoptive transfer of anti-OVA TCR-transgenic T cells and immunization of mice

Splenocytes and lymph node cells from DO11.10 BALB/c mice in which >80% of CD4+ T lymphocytes are specific for OVA were pooled. A total of 30 x 10⁶ DO11.10 cells was i.v. injected into syngeneic wild-type or nude BALB/c mice (Charles River Laboratories, Saint Germain sur l’Arbresle, France). The next day, recipient mice were immunized by injecting s.c. into hind footpads 50 μl of either OVA or keyhole limpet hemocyanin (KLH; Sigma-Aldrich, St Louis, MO) emulsified in CFA at 1 μg/μl. To monitor T cell proliferation in vivo, DO11.10 cells were incubated with CFSE (Molecular Probes, Eugene, OR) at room temperature...
for 10 min and subsequently washed prior to their transfer into recipient mice. CFSE dye dispersing was analyzed by cyttofluorometry in anti-OVA TCR-transgenic T cells tracked with the specific anti-clonotypic KJ1-26 mAb (13, 14).

**Measurement of nociception**

Mechanical withdrawal thresholds were measured using calibrated von Frey filaments of binding forces ranging from 0.04 to 2 g (Stoelting, Wood Dale, IL), applied onto the plantar surface of mice. Ascending series of von Frey filaments were applied, each monofilament being tested five times. Threshold to mechanical stimuli was calculated as the force value of the von Frey filament triggering three paw withdrawals over five applications. Responses to mechanical stimuli were recorded before, and daily after immunization. Naloxone methiodide was injected into the ankle of the inflamed hind paw at a dose of 20 μg in 10 μl PBS, 30 min prior to pain assessment. All experiments involving animals were performed in accordance with ethical guidelines (INSERM) and were approved by the local ethics committee (Midi-Pyrénées, France).

**Preparation of immune cell subsets**

B lymphocytes as well as CD4+ and CD8+ T lymphocytes were purified from total spleen cells by using cell-negative isolation kits (Invitrogen Dynal AS, Oslo, Norway). CD4+ and CD8+ subsets of T lymphocytes were activated by anti-CD3 (clone 145-2C11) and anti-CD28 (clone 37.51) Abs coated at 2.5 μg/ml in culture dishes for 7 d. B lymphocytes were activated with 20 μg/ml LPS for 18 h. Dendritic cells (DCs) and macrophages were generated from bone marrow cells cultured in RPMI 1640, 10% FCS containing GM-CSF (DCs) or M-CSF (macrophages) for 9 d. Cells were activated by adding 1 μg/ml LPS for the last 18 h of culture.

**Cytotofluorometric analysis**

Cells were incubated with optimal concentrations of Abs for 30 min at 4°C in PBS containing 1% FCS and 2 mM EDTA. The mAbs against mouse cell surface Ags were as follows: anti-CD3 (clone 145-2C11), anti-CD4 (clone RM4-5), anti-CD8 (clone 53-6.7), anti-CD25 (clone PC61.5), anti-CD11c (clone II/41), anti-CD11b (clone M1/70), anti-CD69 (clone H1.2F3). All the mAbs were purchased from eBioscience (San Diego, CA). Data were collected on 10,000 living cells by forward and side scatter intensity on a FACSCalibur flow cytometer (BD Biosciences, Franklin Lakes, NJ), and were subsequently analyzed using the FlowJo software (Tree Star, Ashland, OR).

**Immunocytochemistry**

Cells were centrifuged onto glass coverslips for 5 min at 750 rpm in a cytocentrifuge. Cells were fixed in 4% parafomaldehyde for 20 min at room temperature, washed with PBS, and then permeabilized with 0.5% Triton X-100 for 30 min at room temperature. After extensive washing with PBS, cells were incubated with PBS containing 5% FBS for 1 h at room temperature. Rabbit anti–Met-enkephalin polyclonal IgG Abs or normal rabbit control IgG (Chemicon International, Temecula, CA) were then added for 3 h at room temperature. After washing with PBS, cells were incubated with FITC-labeled swine anti-rabbit Fc-specific Ab (DakoCytomation, Glostrup, Denmark) for 1 h at room temperature. Fluorescence images were taken using an upright laser scanner confocal microscope (Carl Zeiss MicroImaging GmbH) with ×100 oil immersion objective.

**PCR analysis**

Total RNA was isolated by TRIzol reagent (Invitrogen, Carlsbad, CA). RNA was reverse transcribed with Moloney murine leukemia virus reverse transcriptase using random hexamer oligonucleotides for priming. Transcript encoding for hypoxanthine phosphoribosyltransferase (HPRT), proenkephalin (PENK), proopiomelanocortin (POMC), and prodynorphin (PYN) were quantified by real-time PCR. Amplification was performed with a Light Cycler 480 (Roche Applied Science, Meylan, France) using SYBR Green I Master (Roche Diagnostics) and the following forward and reverse primers: 5′-GTTCTTGTGACCTGTCGGTGA-3′ and 5′-CCCCC-GTTGACTGATCAATTACAG-3′ for HPRT, 5′-CGACGACATATTACCTG-GCCG-3′ and 5′-AGACGTCAGTGTCGCCCA-3′ for PENK, 5′-TGGCCTGCTGTCAG-3′ and 5′-CAGCGAGAGCTTGGTC-3′ for POMC, and 5′-TGTTGGCAGTGGATTACAG-3′ and 5′-AGACCGTG-CAGGGTGAGAAAGA-3′ for PDNY. The target gene expression was normalized to the HPRT mRNA and quantified relative to a standard cDNA (calibrator sample) prepared from mouse brain, using the 2−ΔΔCt method, where ΔΔ cycle threshold (Ct) = ΔCt sample − ΔCt calibrator. All the primer pairs did not amplify genomic DNA. Sequence analysis of PCR products revealed 100% identity with the corresponding referential cDNA sequence.

**Results**

T cell deficiency results in an increased sensitivity to inflammatory pain in immunized mice

The role of T cell-mediated immunity in regulation of inflammatory pain was first appreciated by comparing nociceptive response to mechanical stimuli using calibrated von Frey filaments in wild-type and T cell-deficient nude BALB/c mice immunized with OVA emulsified in CFA. Basal mechanical sensitivity measured in contralateral nonimmunized control hindpaws was identical in both groups of mice (Fig. 1). Injection into hind paws of OVA emulsified in CFA resulted in a similar increase in sensitivity to mechanical stimuli in both nude and wild-type BALB/c mice. On day 6 after immunization, CFA-induced hyperalgesia started to decrease in immunocompetent BALB/c mice, whereas it remained unchanged until day 9–10 in T cell-deficient nude BALB/c mice. From days 7 to 10, nociceptive response induced by mechanical stimuli was significantly lower in immunocompetent wild-type BALB/c mice, as compared with T cell-deficient nude BALB/c mice (two-way ANOVA analysis, F = 22.36, p < 0.0001, OVA-primed wild-type mice versus OVA-primed nude mice). T cell-deficient nude BALB/c mice recovered their basal sensitivity to mechanical stimuli (i.e., similar to that measured in nonimmunized contralateral hind paw) at day 14. CFA-induced inflammatory pain was worsened in Ag-primed immunocompetent BALB/c mice that have been locally administered with naloxone methiodide, an antagonist of the three classes of opioid receptors unable to cross the blood-brain barrier, indicating that the spontaneous antinociceptive activity is mediated through activation of opioid receptors expressed on peripheral afferent sensory neurons (Fig. 1) (two-way ANOVA analysis, F = 22.15, p < 0.0001, untreated versus naloxone-treated OVA-primed wild-type BALB/c mice). By contrast, mechanical pain sensitivity of OVA-primed nude mice was not altered by naloxone methiodide treatment, indicating that T lymphocytes are the main mediators of opioid-induced analgesia that spontaneously occurred at the sixth day after Ag priming in immunocompetent BALB/c mice (Fig. 1).

**CD4+ T lymphocytes specifically primed by Ag induce analgesia via peripheral opioid receptor activation**

To determine whether the antinociceptive activity of T cells was an effector property specifically acquired in response to Ag, OVA-specific CD4+ T lymphocytes from DO11.10 mice were passively transferred into syngenic recipient nude mice prior to their immunization with either OVA or KLH in CFA. As shown in Fig. 2, the hypersensitive response to mechanical stimuli was significantly more rapidly reduced in mice immunized with OVA, as compared with those immunized with the irrelevant control Ag KLH (two-way ANOVA analysis, F = 6.497, p = 0.018, OVA-primed mice versus KLH-primed mice). The T cell-mediated analgesia only observed in mice immunized with relevant Ag was reversed by neutralizing peripheral opioid receptors with naloxone methiodide (Fig. 2).

**PENK mRNA is upregulated in Ag-primed CD4+ T lymphocytes in vivo**

Because neutralization of analgesia by naloxone methiodide (Fig. 2) suggested a local release of endogenous opioids, we investigated whether opioids were produced by T lymphocytes in re-
response to Ag in vivo. Naive T lymphocytes from DO11.10 mice labeled with the fluorescent CFSE dye were passively transferred into syngeneic BALB/c mice prior to their immunization into hind footpads with OVA or KLH. Cells were recovered from popliteal and inguinal draining lymph nodes on days 1–3 after Ag priming. As shown by the gradual decrease in CFSE fluorescence intensity, KJ1-26+ anti-OVA T lymphocytes proliferated in response to OVA, but not to KLH (Fig. 3A). To compare their ability to produce opioid peptides, KJ1-26+ CD4+ anti-OVAT lymphocytes were isolated from draining lymph nodes of mice immunized with OVA or KLH. Anti-OVA T lymphocytes purified by cytofluorometric cell sorting on day 6 following immunization were 100% pure. mRNA encoding for all three endogenous opioid precursors PENK, POMC, and PDYN was then quantified by real-time PCR. To evaluate the relative ability of the cells to produce each family of opioid precursors, PCR conditions were optimized to amplify each opioid precursor cDNA with an identical efficacy (Fig. 4A). Relative mRNA quantification showed that PENK mRNA content is comparatively much higher than POMC and PDYN mRNA in activated CD4+ T lymphocytes (Fig. 4B), even though POMC and PDYN mRNA can be detected in saturating PCR conditions (40 cycles) (Fig. 4C). These data indicate that enkephalins are the main opioid peptides synthesized by activated T lymphocytes. PENK mRNA level was significantly higher in activated anti-OVA T lymphocytes from mice immunized with OVA than in resting anti-OVAT lymphocytes that have not responded to immunization with KLH ($p$, 0.05; Mann–Whitney U test) (Fig. 3B). Thus, PENK mRNA is up-regulated in T lymphocytes upon their Ag-specific activation in vivo. As shown in Fig. 4D, Met-enkephalin–containing peptides accumulate within cytoplasm of the cells.

Activated CD4+ T lymphocytes are the main source of immune-derived opioids

We compared the relative ability of the main cellular components of the adaptive immune response to synthesize opioids. The expression level of mRNAs encoding for all three opioid precursors was quantified by real-time PCR in DCs (CD14+/CD11c+) and macrophages (CD14+/CD11b+) derived from bone marrow (>92% pure) and T (CD3+/CD4+ or CD8+) and B (B220+/IgM+) lymphocytes isolated from spleen (>89% pure). LPS-induced activation of DCs, macrophages, and B lymphocytes was monitored, respectively, by the upregulation of CD40 plus CD86, F4/80, and...
CD86 at the cell surface. Activation of T lymphocytes by anti-CD3 together with anti-CD28 Abs was checked by the upexpression of CD25 and CD69 molecules (Fig. 5). In our quantitative PCR conditions, PENK, but not POMC and PDYN, was detected, suggesting that PENK-derived enkephalins are the main endogenous opioids produced by immune cells in mice. In resting conditions, PENK mRNA was found in CD4+ T lymphocytes, macrophages, and DCs, whereas it was virtually absent in B and CD8+ T lymphocytes. PENK mRNA was only increased upon activation of DCs and CD4+ or CD8+ T lymphocytes (Fig. 5). PENK mRNA level was significantly higher in activated CD4+ T lymphocytes than in all the other immune cells (one-way ANOVA analysis, \( p < 0.001 \)).

**Discussion**

Our study highlights analgesia as a property linked to the effector phase of adaptive T cell response and identifies effector CD4+ Th lymphocytes generated in response to Ag as a major source of opioids of hematopoietic origin. Thus, in addition to their effector immune functions devoted to the eradication of pathogens, Ag-primed effector CD4+ T lymphocytes also locally release opioids to relieve inflammatory pain.

Somatic pain induced by immunization with Ag emulsified in CFA more rapidly decreases in wild-type mice than in T cell-deficient nude mice. In agreement with a number of previous studies showing that somatic pain can be counteracted by local opioid release by leukocytes (1, 2, 4), neutralization of opioid receptors in periphery by naloxone methiodide worsened CFA-induced pain in Ag-primed wild-type mice. Thus, analgesia that spontaneously occurs on day 6 after immunization in immunocompetent mice, able to develop an adaptive T cell response to Ag, is mediated through activation of opioid receptors expressed on peripheral afferent sensory neurons.

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**FIGURE 3.** PENK mRNA is upregulated in Ag-primed CD4+ T lymphocytes in vivo. A, DO11.10 cells labeled with CFSE dye were transferred i.v. into nonirradiated syngeneic BALB/c mice. The next day, mice were primed s.c. into hind footpads with either KLH (upper panels) or OVA (lower panels) in CFA. Popliteal and inguinal lymph node cells were isolated 1, 2, and 3 d after Ag priming. The figure depicts in the two groups of mice (\( n = 9; 3 \) mice per day) for each day a representative cytofluorometric analysis of CFSE fluorescence distribution in OVA-specific T lymphocytes stained with anti-TCR KJ1-26 mAb. B, Draining lymph nodes were excised from mice on day 6 after priming with KLH (\( \bullet, n = 4 \)) or OVA (\( \circ, n = 4 \)). CD4+KJ1-26+ lymphocytes were purified from total lymph node cells by cytofluorometric cell sorting using anti-CD4 and anti-TCR KJ1-26 mAbs. PENK mRNA was quantified by real-time quantitative PCR in the anti-OVA CD4+ T cell preparation (100% pure). mRNA content was normalized to the HPRT mRNA and quantified relative to standard mouse brain cDNA using the \( 2^{-\Delta\Delta CT} \) method. Gene expression in each sample was assessed in three independent experiments run in duplicate. Results (mean \( \pm \) SEM) are expressed relative to PENK mRNA expression in the mouse brain. Statistical analysis was performed with the Mann–Whitney U test.

CD86 at the cell surface. Activation of T lymphocytes by anti-CD3 together with anti-CD28 Abs was checked by the upexpression of CD25 and CD69 molecules (Fig. 5). In our quantitative PCR conditions, PENK, but not POMC and PDYN, was detected, suggesting that PENK-derived enkephalins are the main endogenous opioids produced by immune cells in mice. In resting conditions, PENK mRNA was found in CD4+ T lymphocytes, macrophages, and DCs, whereas it was virtually absent in B and CD8+ T lymphocytes. PENK mRNA was only increased upon activation of DCs and CD4+ or CD8+ T lymphocytes (Fig. 5). PENK mRNA level was significantly higher in activated CD4+ T lymphocytes than in all the other immune cells (one-way ANOVA analysis, \( p < 0.001 \)).

**FIGURE 4.** Met-enkephalin–containing peptides are highly expressed in Ag-primed CD4+ T lymphocytes in vivo. Opioid precursor mRNA quantification is depicted in A and B, as follows. A, Quantitative PCR standard curves for the POMC, PENK, PDYN, and HPRT genes. For each gene, PCR products that have been previously amplified using specific forward and reverse primers were used as standard cDNA. The figure depicts 10X serial dilution of standard cDNA molecules. Each point of dilution represents the mean of triplicate. B, Two-time serial diluted cDNA sample curve. Total RNA extracted from anti-OVA KJ1-26+ CD4 T lymphocytes purified from OVA-primed mice was reverse transcribed and then amplified with specific primers for POMC, PENK, PDYN, and HPRT genes. C, PCR products amplified for 40 cycles from cDNA samples diluted 10-fold were run in 2% agarose gel. D, Immunochemical detection of Met-enkephalin–containing peptides in anti-OVA KJ1-26+ CD4 T lymphocytes purified from OVA-primed mice. Cells were incubated with either normal control rabbit IgG (\( D, left \) panel) or anti–Met-enkephalin rabbit IgG (\( D, right \) panel). Bound IgG were revealed using FITC-labeled swine anti-rabbit Fcγ-specific Abs. Cell nuclei were stained in blue with DAPI (inset). Fluorescence images were acquired by confocal microscopy. Original magnification \( \times 63 \).
Nociceptive response of OVA-primed nude mice remained unchanged following naloxone methiodide treatment. The similar nociceptive behavior of nude mice displaying or not functional peripheral opioid receptors indicates that analgesia occurring a few days after immunization in immunocompetent mice is primarily dependent on T lymphocytes. Interestingly, within the first 4 d following CFA-induced inflammation, the number of opioid receptors expressed on primary sensory neuron terminals increases (15). This increase in the number of opioid receptors together with the disruption of the perineurium and the enhancement of G protein coupling improve the efficacy of opioid peptides (15, 16).

We then determined whether the antinociceptive activity was specifically acquired by T lymphocytes in response to Ag. OVA-specific CD4+ T lymphocytes from DO11.10 mice were passively transferred into nude mice that have been subsequently immunized with either OVA or KLH in CFA. Analgesia was only observed following CFA-induced inflammation, the number of opioid receptors expressed on primary sensory neuron terminals increases (15). This increase in the number of opioid receptors together with the disruption of the perineurium and the enhancement of G protein coupling improve the efficacy of opioid peptides (15, 16).

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FIGURE 5. PENK mRNA is mainly expressed in activated T lymphocytes and mature DCs. PENK mRNA expression was quantified by real-time PCR in immune cell subsets. CD4+ T lymphocytes (CD3+/CD4+ double-positive cells), CD8+ T lymphocytes (CD3+/CD8+ double-positive cells), and B lymphocytes (B220+/IgM+ double-positive cells) were isolated from spleen of normal BALB/c mice. Macrophages (MO; CD14+/CD11b+ double-positive cells) and DCs (CD14+/CD11c+ positive cells) were derived from bone marrow of normal BALB/c mice. CD4+ T and CD8+ T lymphocytes were activated by using anti-CD3 Abs together with anti-CD28 Abs. B lymphocytes, macrophages, and DCs were stimulated with LPS. The activated status of the cells was testified by the upregulation of CD25 and CD69 on T lymphocytes, CD86 on B lymphocytes and DCs (in addition to CD40), and F4/80 on macrophages. PENK mRNA expression was quantified in unactivated (□) and activated (■) cells. mRNA content was normalized and quantified, as above. Gene expression was assessed in duplicate in at least four independent cell preparations. Data (mean ± SEM) are expressed as percentage of PENK mRNA content in the mouse brain.

CD4+ T cell-dependent analgesia observed in OVA-primed mice is dependent on peripheral opioid receptors outside the CNS, as the analgesic effect was inhibited by an opioid receptor antagonist that does not cross the blood-brain barrier. The antinociceptive activity associated with the generation of effector CD4+ T lymphocytes in response to Ag is thus elicited by local release of opioids within the inflammatory site. In agreement, PENK mRNA synthesis is 7-fold increased in CD4+ T lymphocytes that have responded to Ag compared with resting CD4+ T lymphocytes that have not responded to Ag in vivo. By contrast, POMC and PDYN mRNA are barely detectable in effector CD4+ T lymphocytes in response to Ag. Thus, the decrease in nociceptive sensitivity that spontaneously occurs a few days after Ag priming is most likely dependent on enkephalin release by Ag-primed CD4+ T lymphocytes.

Exposure to infectious agents induces an early inflammatory reaction causing painful sensation. Inflammatory mediators via DC maturation contribute to initiation of adaptive T cell immune response that in turn will enhance the innate host defense capabilities. In this context, pain could be apprehended as a biological danger
alert signal that will decrease in parallel to the mobilization of Ag-specific effector T lymphocytes within the inflammatory site. Common skin infections such as cellulitis caused by staphylococci or streptococci are often associated with painful sensation. As a matter of fact, pain is a common symptom associated with infections that occurs more often in immunodepressed individuals, including AIDS patients. Given the antinociceptive effect of Ag-specific effector CD4+ T lymphocytes, our study suggests that pain relief, which occurs before the resolution phase of inflammation, is the sign of an active T cell response at the inflammatory site. The role of immune T cell response in other chronic pain situations induced in the absence of infections (i.e., in the absence of CFA) remains to be determined.

The production of opioids has been described in most of the hematopoietic cells (4, 14, 18, 19), but our results, in line with others (5, 11, 12), suggest that effector memory T lymphocytes are more efficient to relieve inflammatory pain. These results suggest that the potency of immune cells to produce opioids is probably not similar have been testified by quantifying the relative ability of the main cellular components of the adaptive immune response to synthesize all three opioid precursors. In resting conditions, CD4+ T lymphocytes, macrophages, and DCs, but not B lymphocytes and CD8+ T lymphocytes, express PENK mRNA. Cell activation upregulates PENK mRNA in DCs, CD4+ T lymphocytes, and CD8+ T lymphocytes. PENK mRNA level, which is higher in activated CD4+ T lymphocytes than in all other immune cell subsets, may reach >50% of that measured in brain, used as reference. In our quantitative PCR conditions, POMC and PDYN were never detected in all immune cell subsets that have been examined. Thus, in vitro quantification of the relative endogenous opioid content in immune cells confirms that enkephalins are mainly produced by activated CD4+ T lymphocytes that play a major role in endogenous pain regulation.

In line with the predominant production of enkephalins by effector T lymphocytes in vivo, it has been recently shown that 6-type opioid receptor, which exhibits more affinity for enkephalins, can be mediated by opioid receptors expressed on peripheral sensory fibers and, therefore, free of side effects has opened new therapeutic perspectives for pain treatment (27). These results highlight CD4+ Th lymphocytes as major actors of endogenous pain modulation in chronic inflammatory disorders. Considering CD4+ Th lymphocytes as cellular targets for the treatment of chronic inflammatory disorders might thus be re-estimated in light of their major role in controlling inflammatory pain.

Disclosures

The authors have no financial conflicts of interest.

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