Expression of the pancreatitis-associated protein I (PAP I), an exocrine pancreatic protein, increases rapidly and strongly in acinar cells during the acute phase of pancreatitis. This is reminiscent of the response to stress of acute phase proteins. We have previously demonstrated that serum factors from rats with acute pancreatitis, but not from healthy rats, could induce endogenous PAP I gene expression in the acinar cell line AR-42J (Dusetti, N., Mallo, G., Dagorn, J.-C., Iovanna, J. L. (1994) Biochem. Biophys. Res. Commun. 204, 238-243). In the present work, we have evaluated the influence of several mediators of inflammation on rat PAP I gene transcription in these cells. Tumor necrosis factor α induced an increase in PAP I mRNA expression, and interferon γ caused an even greater increase in PAP I mRNA level. These stimulations were antagonized by dexamethasone. Interleukin (IL)-1, IL-6, or dexamethasone alone were ineffective. Combinations of IL-1 with IL-6 or dexamethasone were also ineffective. IL-6 and dexamethasone together induced a marked stimulation of PAP I gene transcription, and this effect was slightly attenuated by IL-1. To analyze the cis-regulatory elements responsible for the induction of transcription, we fused a 1.2-kilobase segment of the rat PAP I promoter to the chloramphenicol acetyltransferase (CAT) gene as reporter. The resultant chimeric DNA was transfected into AR-42J cells. Addition of IL-6 or dexamethasone was ineffective, whereas their mixture increased the CAT activity 12 times. Progressive deletions of the PAP I promoter were then fused to the CAT gene, and the constructs were transfected to AR-42J cells. A 12-fold increase in CAT activity was seen upon IL-6/dexamethasone treatment with constructs containing more than 274 base pairs upstream from the cap site. In that region, two sequences are similar to the canonical IL-6 response element. Site-directed mutagenesis of these regions strongly decreased induction, showing that they were functional. PAP I should therefore be classified among acute phase proteins of class 2, whose expression is increased by IL-6 acting in combination with glucocorticoids.

The acute phase of pancreatitis is characterized by a pattern of changes in the expression of secretory proteins (1). Whereas expression of most pancreatic enzymes decreases, mRNA levels of the rat pancreatitis-associated protein (PAP) increase dramatically. Recently, we have described two other PAP-related mRNAs and named the corresponding proteins PAP II and PAP III (2, 3). In consequence, the original PAP became PAP I. Like PAP I, PAP II and III are induced in pancreas during the acute phase of pancreatitis. The sequences of the genes encoding rat PAP I, II, and III have been recently determined (2, 4, 5). All three genes are organized in six exons, and similarities observed in their coding sequences extend to their 5’-flanking regions. In addition, the three genes have been located to the same position on chromosome 4q33–34 (6), suggesting that they derived from the same ancestral gene by gene duplication.

In fact PAP I was not detectable in the pancreas of healthy animals. It could be evidenced in pancreatic juice 6 h after induction of an experimental acute pancreatitis, reached a maximum during the acute phase (12–48 h), and disappeared during recovery (7). The rapid and strong induction of the PAPs is unique among secretory proteins and reminiscent of the response to stress of acute phase proteins. Recently, we have demonstrated the presence of factors in serum from rats with acute pancreatitis, but not from healthy rats, capable of inducing PAP I gene expression in the pancreatic acinar cell line AR-42J. In addition, the cis-acting element was localized within the 1.2 kilobases upstream region of the transcription start site (8). It has long been known that the changes occurring in the liver and in other organs during the acute phase response are coordinated by signals generated at the site of injury, among which several cytokines have been well characterized, including IL-1, IL-6, TNFα, IFNγ, leukemia inhibitory factor, IL-11, and oncostatin M. These proteins are locally produced by the tissue and by circulating mononuclear cells in response to prototype inflammatory stimuli and can elicit the diverse biological effects characteristic of the acute phase response. Interestingly, during the acute phase of pancreatitis, levels of cytokines are strongly increased in serum (9). In the current study, we have evaluated the respective contributions of several cytokines and of dexamethasone to the transcriptional induction of the rat PAP I gene in vitro, using a rat pancreatic acinar cell line.

**EXPERIMENTAL PROCEDURES**

AR-42J Stimulation—AR-42J pancreatic acinar cells were obtained from Dr. A. Estival (INSERM U151, Toulouse, France) and used after 42–49 passages. The cells were routinely cultivated at 37 °C in a 5%
CO₂, 95% air atmosphere in Dulbecco's modified Eagle's medium containing 10% (v/v) fetal calf serum (Life Technologies, Inc.), 4 mM l-glutamine, 50 units/ml penicillin, and 50 mg/ml streptomycin. The cells were seeded at 3 × 10⁵/100-mm Petri dish. When cells reached 80–90% confluence (which took approximately 1 week), they were dissociated with 0.05% trypsin and 0.02% EDTA in Puck's saline A and replated.

For the transfection experiments, cultures were incubated with either control medium, IL-1, IL-6, IFN-γ, TNF-α, dexamethasone, or a combination thereof. After 48 h, the medium was removed and replaced with fresh medium containing the indicated amount of the stimulant. Twenty-four hours later, total cellular RNA was prepared by the acidic guanidium thiocyanate phenol-chloroform extraction method (10). Total cellular RNA (15 μg/lane) was fractionated by electrophoresis on a 1.0% agarose-formaldehyde gel and transferred onto nylon filters (Hybond). Filters were then hybridized with 3²P-labeled probes for rat PAP I (7) and β-actin (8). Filters were then washed extensively and autoradiographed.

**CAT Reporter Gene Constructs**—All DNA constructs were generated by polymerase chain reaction using the plasmid P/P as a template (4). That plasmid is a pBluescript KS+ in which was subcloned a 2859-base pair PstI-PstI genomic DNA fragment containing the PAP I gene, including 1253 nucleotides of the promoter. Accuracy of polymerase chain reaction reaction was increased by using low dNTP concentrations (11), 100 ng of DNA plasmid as template, and only eight cycles of DNA amplification. Amplification was performed in 1 x polymerase chain reaction buffer (50 mM KCl, 10 mM Tris-HCl, pH 8.3, 2 mM MgCl₂, and 0.01% gelatin) containing 2 μM dNTP, 1% Me₂SO, 25 pmol of each primer, and 2.5 units of Taq polymerase in a final volume of 50 μl. The reaction times were as follows: first cycle, denaturation at 94 °C for 2 min, annealing at 55 °C for 2 min, and extension at 74 °C for 2 min; for the next 6 cycles, denaturation at 94 °C for 10 s, annealing at 55 °C for 2 min, and extension at 74 °C for 2 min; for the last cycle, denaturation at 94 °C for 10 s, annealing at 55 °C for 2 min, and extension at 74 °C for 10 min. The product was blunted-ended with Klenow polymerase, kinased, and ligated into the SalI site of the promoterless vector pCAT-Basic (Promega) to generate the plasmids p-1253/+10PAPI-CAT, p-926/+10PAPI-CAT, p-685/+10PAPI-CAT, p-444/+10PAPI-CAT, p-317/+10PAPI-CAT, p-274/+10PAPI-CAT, p-180/+10PAPI-CAT, p-118/+10PAPI-CAT, p-61/+10PAPI-CAT, and p+10/+1253PAPI-CAT. Mutant plasmids were also constructed, to monitor the function of two sequences in the PAP I promoter corresponding to potential IL-6 response elements. Plasmids pmut1-274/+10PAPI-CAT, pmut2-274/+10PAPI-CAT, and pmut3-274/+10PAPI-CAT were generated, in which IL-6RE-1, IL-6RE-2 or both were modified, respectively (Fig. 5). The following oligonucleotides were used: 5'-CCCTTGTGTTAGAAACACAGTATCTGGAAAAGGGTG-TGGAGGGTTTCAAAC-3', 5'-CCCTTGTGTTTCCCCAGACAGCATATAGTGAGGGTTTCAAAC-3', and 5'-CCCTTGTGTTGAGAAACAGTATCTGGAAAAGGGTG-GAGAGGTTTCAAAC-3'. The underlined sequences corresponding to positions of first and last nucleotides of the insert in the PAP I gene. Plasmid DNA was purified with the Qiagen plasmid Kit (Qiagen, Hilden, Germany) and the DNA concentration measured spectrophotometrically. Sequences were verified by the chain termination method using the 17 sequencing kit (Pharmacia Biotech Inc.). Plasmids were also checked for purity, concentration, supercoiling, and restriction pattern by agarose gel electrophoresis.

**Cell Transfection and CAT Assays**—Fifty to 60% confluent AR-42J cells in culture, cytokines and dexamethasone, alone or in combination, were added to the culture medium. After 24 h total RNA was isolated, submitted to electrophoresis (15 μg/lane) through a formaldehyde-agarose gel, transferred to a nylon membrane, and hybridized to 3²P-labeled cDNAs specific for the PAPI and β-actin mRNA. Results for IL-1, IL-6, and dexamethasone are given in panel A. Results for IFN-γ, TNF-α, and dexamethasone are given in panel B; results with dexamethasone and the combination IL-6/dexamethasone, from an experiment run in parallel, are given as controls. Concentration of cytokines and dexamethasone are provided in the corresponding tables. Lanes 7 and 13 in panel A and lane 9 in panel B refer to experiments where no cytokines or dexamethasone were added.

**Results**

**Effect of IL-1, IL-6, IFN-γ, TNF-α, and Dexamethasone on AR-42J PAP mRNA Levels**—AR-42J is a pancreatic tumor cell line derived from an azaserine tumor of the rat exocrine pancreas (14), which has retained most characteristics of the acinar cells. In these cells, the basal level of the PAP I transcript is extremely low, as in normal pancreas (4). We have monitored PAPI mRNA expression following treatment with several cytokines and dexamethasone. As shown in Fig. 1, treatments with IL-1 (50 and 500 units/ml), IL-6 (100 and 1000 units/ml), or dexamethasone (10 and 100 nM) alone were ineffective. Treatment with TNF-α (500, 1000, and 5000 units/ml) or IFN-γ (100, 500, and 1000 units/ml) induced weak PAPI mRNA expression by comparison with untreated cells. However, dexamethasone clearly inhibited their stimulatory effects. Combinations of IL-1 with IL-6 or dexamethasone were also ineffective. By contrast, combination of IL-6 with dexamethasone induced a strong stimulation of PAPI gene transcription and subsequent mRNA accumulation. Surprisingly, when IL-1 was added together with IL-6 and dexamethasone, the induction was partially inhibited. The extremely low basal level of PAPI expression in AR-42J cells and the strong signal observed in Northern blots upon stimulation suggest that PAPI gene expression in these cells is primarily controlled by transcriptional regulation. Differences in β-actin mRNA concentrations were mainly due to differences in total RNA on the filters, estimated from methylene blue coloration.

Analysis by Progressive Deletion of Sequences Required for IL-6/Dexamethasone Induction of PAPI I Gene—The presence of a functional promoter and tissue-specific elements in the
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5'-flanking region of the rat PAP I gene was tested by transient expression assays. A 1253-base pair fragment containing the PAP I 5' region was fused to the bacterial gene coding for chloramphenicol acetyltransferase (bacterial) whose expression can be easily monitored in transfected cells. Transfection experiments showed that p-1253/+10PAPI-CAT was able to promote basal transcription in AR-42J cells (8). Fig. 2 shows the comparison of CAT activity in extracts from AR-42J cells transfected with the above constructs, then stimulated with IL-6, dexamethasone, or IL-6 and dexamethasone. Treatments with IL-6/dexamethasone increased CAT activity 12 times, whereas IL-6 or dexamethasone alone were ineffective. In order to identify the regions necessary for IL-6/dexamethasone induction, progressive deletions of the PAP I promoter were performed, and the resulting constructs were transfected into AR-42J (see "Experimental Procedures"). As shown on Fig. 3, deletions in the 5' to 3' direction resulted in a stepwise decrease of CAT activity in the AR-42J cell line. Deletion down to position −926 did not alter significantly the expression of the reporter gene. Deletion to nucleotide −685 resulted in about 30% decrease in expression. Progressive deletion of the next 368 nucleotide (to position −317) did not alter CAT activity further. An additional deletion to nucleotide −274 caused a decrease to 40% of the control. Extending deletion to nucleotide −180 decreased expression by 20% of the control, and a further deletion of 62 base pairs (to position −118) resulted in a reduction of the CAT activity to about 10% of control. Finally, deletion down to nucleotide −61 further reduced activity about 3 times, although it remained slightly above background.

A 12-fold increase in CAT activity was seen upon IL-6/dexamethasone treatment of cells transfected with constructs containing more than 274 base pairs of 5'-flanking sequence (Fig. 4). Deletion to position −180 led to a 3-4 fold drop in induction. Finally, a 2-fold induction was observed when we transfected with p−118/+10PAPI-CAT and p−61/+10PAPI-CAT constructs but not with p+10−1253PAPI-CAT.

Mutation Analysis Reveals Two Functional IL-6 Response Elements (IL-6RE) in the PAP I Promoter Region—Computer-assisted search for sequences similar to previously described IL-6RE showed two potential regions within the PAP I promoter, at positions −266 to −260 (in antisense orientation) and −249 to −243 (in sense orientation). To analyze these sequences, site-directed mutagenesis of the regions from −266 to −260 and −249 to −243 was conducted within the CAT construct p−274/+10PAPI-CAT and the influence of the mutations on the amplitude of CAT induction by IL-6/dexamethasone was monitored. With mutant pmu1−274/+10PAPI-CAT, in which the sequence from −266 to −260 was modified, induc-
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**Fig. 5. Identification of two functional IL-6REs within the PAP I promoter by site-directed mutagenesis.** A, nucleotide substitutions in p–274/+10PAPI-CAT plasmid B, AR-42J cells were transfected with 20 μg of plasmids p–274/+10PAPI-CAT, pmut1-274/+10PAPI-CAT, or pmut2-274/+10PAPI-CAT. Thirty-six hours after transfection of AR-42J cells, IL-6 (100 units/ml) and dexamethasone (100 nM) were added to the culture medium. Cells with no hormones added were taken as controls. Specific induction by IL-6/dexamethasone was calculated as the ratios of the values from induced and control cells. Values represent the means (± standard error) of six independent transfection experiments.

The cytokines tested in this study had very different effects on PAP I gene expression in AR-42J cells (Fig. 1). The most striking result was the strong stimulation of the association of IL-6/dexamethasone, and the limited stimulation by IFNγ or TNFα, compared to the absence of effects of IL-1 or IL-6. Another intriguing finding was the inhibition by IL-1 of IL-6/dexamethasone stimulation. However, a growing number of reports show that expression of acute phase protein genes is not always mediated by single cytokines but by combinations of several cytokines (15–17) or by cytokines in association with cofactors such as glucocorticoids (16). It was also shown that one cytokine may modulate the effect of other cytokines (17, 18). These findings suggest that specific responses of a cell to various inflammatory stimuli are mediated by specific combinations of cytokines and/or glucocorticoids. Although an important regulatory function during the acute phase reaction has been attributed to glucocorticoids and IL-6 (17), at the utilized doses, dexamethasone and IL-6 alone were unable to induce PAP I gene expression in AR-42J cells (Figs. 1 and 2). Thus, two mechanisms may account for the synergy between IL-6 and dexamethasone. First, glucocorticoid and IL-6 response elements might be localized in close vicinity on the PAP I promoter. In that instance, interaction of the nuclear factors binding the two transcription activator elements might enhance individual responses that would be otherwise too weak to be observed. Such a situation was reported for the α1-acid glycoprotein (19). Second, dexamethasone could stimulate IL-6 receptor synthesis in AR-42J cells, resulting in an increased number of IL-6 receptors at the cell surface. This was already observed in hepatic cells (20, 21). That mechanism might apply to the PAP I gene since, in the hepatic carcinoma cell line HepG2 transfected with p–1253/+10PAPI-CAT, CAT activity could be strongly induced (25-fold) by IL-6 alone (data not shown). Hence, the IL-6 enhancer element of the PAP I promoter does not require glucocorticoids to be active. More studies are, however, necessary to understand the synergistic effect of IL-6 and dexamethasone on the PAP I gene induction in AR-42J cells.

The mechanism by which IL-1 down-regulates the stimulation by IL-6 associated with dexamethasone is also unknown. IL-1 has already been shown to inhibit IL-6 induction of the endogenous T kininogen in rat primary hepatocytes (22), but IL-1 and IL-6 can also act independently (additive effect) or synergistically in the regulation of other acute phase genes such as α1-acid glycoprotein, haptoglobin, hemopexin, complement C3, and serum amyloid A (17). Therefore, relative positions of the different enhancer sequences are likely to influence the effect of cytokines acting in combination. A mechanism involving interaction of IL-1 with expression of the IL-6 receptor, as suggested for dexamethasone, cannot be ruled out, although such regulation has never been reported in other systems. However, inhibition by interaction of IL-1 with the IL-6 receptor is unlikely because the two cytokines have their own specific membrane receptors.

PAP I gene expression was significantly induced by IFNγ or TNFα, although 100-fold less than with IL-6 and dexamethasone. Other genes induced by TNFα are also induced by IFNγ (23–25). This may be due to the ability of TNFα and IFNγ to activate the same transcription factors, such as interferon regulatory factors 1 and 2 (26, 27). A similar PAP I mRNA induction was obtained with 100, 500, or 1000 units/ml IFNγ, but an inhibitory effect was observed when we incubated the cells in presence of more than 500 units/ml TNFα (Fig. 1), suggesting a toxic effect of this cytokine. Addition of dexamethasone to these cytokines inhibited induction, as already reported for other genes (28–34). Again, the opposite effect of dexamethasone on IL-6 and TNFα or IFNγ underscores that understanding the mechanism of effector action requires a detailed topological analysis of promoter sequences.

We have chosen to address in this study the molecular mechanism of IL-6 and dexamethasone stimulation of the PAP I promoter. Analysis of the promoter sequence revealed the presence in two positions of the potential IL-6 response element of type 2 (CTGGGA), previously identified in several acute-phase genes (17, 18, 35) and shown to be functional by mutation analysis (36). Demonstration that the two IL-6REs identified in
the PAP I promoter were indeed functional was obtained by mutation and transfection assays (Fig. 5). However, these are not the only cis-elements involved in the IL-6/dexamethasone response of PAP I. Another cis-cytokine response element, localized between −61 and +10, is responsible for a 2-fold induction. This has been shown previously in other IL-6-activated cellular genes (37). For instance, Baumann et al. (38) have demonstrated for several acute phase proteins that IL-6 acts directly through an IL-6RE but also indirectly by increasing expression of C/EBPs, which in turn stimulates acute phase proteins gene expression.

Acute phase proteins have been divided into two subclasses according to their pattern of regulation by cytokines (17). The synthesis of class 1 acute phase proteins (e.g. α2-acid glycoprotein, C-reactive protein, haptoglobin, and serum amyloid A) is mainly regulated by IL-6 and glucocorticoids. PAPI is therefore an additional member of the second group of acute phase proteins, with the original feature of being a secretory protein.

Finally, it is interesting to note that whereas the PAP I gene is expressed as an acute phase protein in pancreas, it is constitutively expressed by the epithelial cells of the intestinal tract (39, 40). The PAPI promoter is therefore complex. It confers to the gene the capacity of being regulated along several pathways, the switch between pathways being possibly under the control of tissue-specific elements.

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