Somatostatin Stimulates Gastrin mRNA Turnover in Dog Antral Mucosa*

Pratima S. Karnik and M. Michael Wolfe‡

From the Harvard Digestive Diseases Center, the Harvard-Thorndike Laboratory and Charles A. Dana Research Institute, Division of Gastroenterology, Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts 02215

Previous studies have demonstrated that antral somatostatin exerts inhibitory effects on gastrin cells via paracrine pathways, accomplished by its release from somatostatin-containing cells into the immediate interstitial environment of the gastrin cell. The present studies were directed to examine the effect of somatostatin on gastrin gene transcription in the dog antrum and to determine whether somatostatin modulates gastrin mRNA turnover. In response to the immunoneutralization of endogenous antral somatostatin, basal gastrin gene transcriptional activity increased by 34 ± 3.3% (p < 0.01). Moreover, somatostatin significantly inhibited gene transcription that had been stimulated by dibutyryl-cAMP and carbachol. To determine the effect of somatostatin on gastrin mRNA turnover, antral mucosal fragments were incubated with antibodies to somatostatin, total RNA was extracted, and gastrin mRNA was measured at several time points. Following the immunoneutralization of antral somatostatin, maximum induction was achieved at 60 min, at which time gastrin mRNA levels had increased by 184 ± 6.0% (p < 0.01). At that time, a somatostatin analogue which is biologically active, but nonimmunoreactive with the antiserum, was added to the incubation medium. The analogue produced a prompt and steady de-induction of gastrin mRNA concentration, which returned to basal levels by 120 min. Regression analysis of RNA induction and de-induction profiles demonstrated a 292 ± 40.6% increase (p < 0.01) in gastrin mRNA turnover induced by somatostatin. In separate experiments antral mucosa was incubated with cycloheximide, both in the presence and absence of somatostatin antibodies. Incubation in the presence of cycloheximide resulted in a 52.3 ± 8.4% (p < 0.01) increase in gastrin mRNA levels under basal conditions, but had no effect following antral somatostatin immunoneutralization. Our results indicate that, although somatostatin inhibits gastrin gene transcription, its predominant effect on gastrin gene expression appears to occur at the posttranscriptional level by increasing the turnover of gastrin mRNA.

The gastrointestinal regulatory peptide gastrin plays a central role in the physiological regulation of gastric acid secretion (1). Following stimulation, the secretion of acid is modulated by a negative feedback loop, in which antral acidification inhibits the further release of gastrin (1). The precise mechanism of this negative feedback loop has not been elucidated, although recent studies have suggested the potential involvement of the polypeptide somatostatin (2–4). Originally identified as an inhibitor of growth hormone (5), somatostatin has been shown to inhibit the release of several regulatory peptides, including gastrin (2, 3). However, the molecular mode of action of somatostatin in these physiological processes has not been clearly and thoroughly defined.

Changes in steady state mRNA levels could theoretically result from altered rates of transcription or from changes in the rates of mRNA turnover. In the present experiments, we have sought to determine the contribution of each of these
parameters to the levels of gastrin mRNA. The results of these studies indicate that under basal conditions somatostatin exerts a small, but significant, inhibitory effect on transcription of the gastrin gene. They show further that somatostatin-mediated effects on antral gastrin cells occur predominantly at the posttranscriptional level, by enhancing the rate of gastrin mRNA turnover.

MATERIALS AND METHODS

Preparation and Incubation of Dog Antral Mucosa—Antral mucosa was obtained from fasting mongrel dogs anesthetized with α-chloralose (Sigma) and was processed as described previously (6, 11, 12). Antral mucosal strips were incubated under control conditions in Krebs-Henseleit bicarbonate buffer (KHB) containing normal rabbit serum at a final dilution of 1:500. The effect of somatostatin on gastrin mRNA levels was examined by immunoneutralization with an addition of specific rabbit somatostatin antibodies to the incubation medium. Somatostatin antiserum 117-3 (generously provided by Dr. J. E. McGuigan, Gainesville, FL) has been fully characterized elsewhere (12) and was used in these experiments at a final dilution of 1:500. The effect of somatostatin on antral gastrin mRNA levels was also tested by the inclusion of somatostatin-14 or the analogues [Leu⁶,α-TyrD-Trp²,TyrL₈]somatostatin-28 (both obtained from Peninsula Laboratories) in the incubation medium. This analogue, although biologically active, is nonimmunoreactive with somatostatin antisera 117-3, and we have recently shown that it is capable of reversing the stimulatory effects produced following intragastric somatostatin immunoneutralization (11). In separate experiments, the effects of cycloheximide and actinomycin D (both purchased from Sigma) on gastrin mRNA levels, in the presence or absence of somatostatin antibodies, were determined. Antral mucosal fragments were harvested at various time points for either total RNA extraction followed by dot blot hybridization, or nuclear isolation.

RNA Extraction—RNA was extracted from antral mucosa using a modification of the method of Mulvihill et al. (13, 14). RNA yields were quantitated by absorption at 260 and 280 nm. A₂₆₀/A₂₈₀ ratios of 1.95-2.0 indicated that the samples were essentially free of contaminating protein.

Isolation of Nuclei and Nuclear Run-off Assays—After a 60-min incubation, nuclei were isolated from antral mucosa using a modification of the method of Mulvihill et al. (15, 16). For the nuclear transcriptional assay, isolated nuclei (70 μl) were incubated with ATP, CTP, and UTP (2 μM each), 0.2 mM GTP, and [α-3²P]GTP (300 μCi) in 0.15 M KCl and 3 mM magnesium acetate. The reaction (200 μl) was continued for 45 min at 25 °C (17, 18). For the detection of specific transcripts, 5-10 μg of plasmid pHS629 (a generous gift from Dr. J. Rehfeld, Copenhagen, Denmark), containing gastrin cDNA was hybridized to the run-off products for 24-36 h. Chicken erythrocyte actin cDNA (donated by Dr. D. Tenen, Boston, MA), ubiquitin cDNA (kindly provided by Dr. K. Lund, Chapel Hill, NC), and plasmids pGEM-3 and pBR322 were used as controls.

Dot Blot Hybridizations—Because the sensitivity of conventional nick-translated cDNA hybridization probes is insufficient to permit the detection of gastrin mRNA from the dog antrum (11), antisense gastrin mRNA probes were generated which enabled us to measure less than 5 pg of gastrin mRNA. A 465-base pair cDNA fragment encoding human gastrin (19) was cloned into the expression vector pGEM-blue (Ribobprobe, Promega Biotec) using standard techniques (20). Labeled antisense gastrin RNA probes were prepared by cleaving with SfcI and transcribing with SP6 polymerase, in the presence of [α-3²P]GTP as described by Melton et al. (21). Dot blot hybridizations were performed using Genescreen Plus filters (Du Pont-New England Nuclear) and relatively stringent conditions, as described by the manufacturer. Autoradiograms were developed after exposure to x-ray film overnight at -70 °C, using a Cronex intensifying screen (DuPont). The hybridization signal was quantified by densitometry and integration of the autoradiographic images using a laser densitometer (model 202, LKB Instruments, Inc., Gaithersburg, MD) to compare gastrin mRNA levels.

Statistical Analysis and Regression Analysis—All results are expressed as the mean ± S.E. of four separate experiments measured in duplicate. Student’s t test for paired samples was used to compare the rates of mRNA transcription obtained during nuclear run-off assays. The t test for unpaired samples was used to compare gastrin mRNA levels obtained under various conditions. Statistical significance was assigned if p < 0.05. The kinetics of induction and de-induction were calculated using the rate equation derived by Berger et al. (22):

\[
\frac{d[R]}{dt} = k_d [R] - k_i [R]
\]

In this equation, \(R_i\) represents the final concentration of gastrin mRNA, \(R_i\) the level of mRNA at a specific time, and \(R_0\) the initial concentration of gastrin mRNA; \(k_d\) and \(k_i\) represent the slopes of the linear plots obtained during induction and de-induction, respectively, in which the natural logarithm of mRNA levels were plotted against time, using computer-derived regression analysis (Sigma-Plot, Jandel Scientific, Corte Madera, CA).

RESULTS

Effect of Somatostatin on Steady State Levels of Gastrin mRNA—Following immunoneutralization of antral somatostatin by the inclusion of specific antibodies to somatostatin in the incubation medium, basal gastrin mRNA concentration increased by 184 ± 6.0% over control (p < 0.01) (Fig. 1). We have shown previously (11) that in response to immunoneutralization, an increase in steady state gastrin mRNA is detectable at 30 min, reaches maximum levels by 60 min, and remains stable over a period of 4 h. When antral mucosa was incubated for 60 min in the presence of 10⁻⁸ to 10⁻⁴ M somatostatin, a concentration-dependent decrease in the levels of gastrin mRNA was detected (Fig. 1). These changes in steady state levels of gastrin mRNA could be due to either alterations in the rate of gene transcription or in the rate of mRNA turnover.

Effect of Somatostatin on Gastrin Gene Transcription—Nuclear run-off transcription assays were performed to determine the relative effect of somatostatin on gastrin gene transcription. In most nuclear transcription systems, mRNA synthesis is due primarily to the elongation of RNA chains (23). Therefore, when isolated nuclei continue mRNA synthesis in vitro, the measurement of specific incorporation of a radiolabeled nucleotide into mRNA provides an accurate reflection of the rate of transcription. To examine the effect of somatostatin on basal levels of gastrin mRNA, antral mucosa was incubated for 60 min in the presence of normal rabbit serum (1:500 final dilution), 10⁻⁶ M somatostatin, or somatostatin antisera 117-3 (1:500 final dilution). To examine the effect of somatostatin on stimulated gastrin gene transcription, antral mucosa was incubated with 10⁻⁴ M N²⁰-D-α-
The use of this analogue can reverse the stimulatory effects of RNA polymerase II and III. The effects of somatostatin on gene transcription were performed by 184 f 6.0% (p < 0.01). At that time, 10^-6 M amanitin, a fungal cyclic peptide that inhibits gene transcription by RNA polymerase II and III, was included in the incubation medium. In contrast, in response to immunoneutralization of antral somatostatin, gastrin gene transcriptional activity increased by 34 ± 3.3% (p < 0.01). The increase in transcription of the gastrin gene was specific, since no significant change in transcription of cytoskeletal actin or ubiquitin could be detected. In addition, no significant hybridization with pGEM-3 or pHK322 (control cDNA) was observed, indicating that the transcription was specific for genomic sequences. When amanitin was included in the incubation medium, transcription of the gastrin, actin, and ubiquitin genes were completely abolished (data not shown).

In response to dbcAMP and carbachol, gastrin gene transcriptional activity increased by 552% (148.0 ± 16.2 ppm) and 229% (74.6 ± 3.1 ppm), respectively (both p < 0.01) (Fig. 2). When 10^-6 M somatostatin was added to the incubation medium containing dbcAMP or carbachol, the increases in the rate of gastrin gene transcription were nearly abolished (Fig. 2). No significant effect on the transcription of either the actin or ubiquitin genes was observed. These results indicate that although exogenously administered somatostatin had no effect on unstimulated gene transcription, the peptide significantly inhibited gastrin gene transcription that had been stimulated by both dbcAMP and carbachol. Moreover, following the withdrawal of the tonic inhibitory control of endogenous somatostatin on antral gastrin cells by immunoneutralization, a small, but significant, increase in the basal rate of gastrin gene transcription was detected. However, the magnitude (34%) of this effect does not appear to constitute the principal contribution to the 184% increase in steady state gastrin mRNA levels detected after antral somatostatin immunoneutralization (Fig. 1).

**Effect of Somatostatin on Gastrin mRNA Turnover**—The kinetics of gastrin mRNA turnover were determined by the incubation of antral mucosal fragments with antibodies to somatostatin (1:500 final dilution), which as shown above eliminates the tonic inhibitory effects of somatostatin on the gastrin cell, thereby generating an induction of gene expression. Because [Leu]-D-Trp^28,Tyr^28]somatostatin-28 is biologically active, but not immunoreactive with the antisera, the use of this analogue can reverse the stimulatory effects of somatostatin immunoneutralization, effecting a de-induction of gastrin gene expression. Total RNA was extracted at several time points during both the induction phase and during de-induction with the somatostatin analogue, and levels of gastrin mRNA were measured by dot blot hybridization.

In response to immunoneutralization of antral somatostatin, a significant increase in gastrin mRNA levels was evident by 30 min (Fig. 3). Maximum induction was achieved at 60 min, at which time gastrin mRNA levels had increased by 184 ± 6.0% (p < 0.01). At that time, 10^-6 M [Leu]-D-Trp^28,Tyr^28]somatostatin-28 was added to the incubation medium. The somatostatin analogue produced a prompt and steady de-induction of gastrin mRNA concentration, which returned to basal levels by 120 min (Fig. 3). The induction and de-induction profiles were reexamined using regression analysis, as indicated above. By plotting the natural logarithm of mRNA levels against time, the k_i (induction) was 0.038, while during de-induction, the k_d was 0.149 (Fig. 4). This difference represents a 292% increase in gastrin mRNA turnover in response to somatostatin.

This indirect method for the determination of gastrin mRNA half-life is based on the assumption that the rate of change from an initial to a final steady state is equivalent to the turnover rate (24). The half-life measurements are not actual, but rather are relative, and also assume that the rates of synthesis and degradation occur rapidly and become constant and that the rates of change of gastrin mRNA levels approach first order kinetics (25). The utilization of these indirect methods for the determination of the relative rates of gastrin mRNA half-life is necessary due to currently inad-

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**Fig. 2.** Rate of gastrin gene transcription following immunoneutralization of antral somatostatin with antibodies to somatostatin (Anti-S), and under basal and stimulated conditions, both in the absence and presence of 10^-6 M somatostatin (STS). Gastrin gene transcription was stimulated with dbcAMP (10^-4 M) and carbachol (10^-5 M). Gene transcription rates are expressed in parts/million (ppm) ± S.E. Nonspecific hybridization to filters containing the plasmid pBR322 (nonspecific hybridization) was ~1-3 ppm and was subtracted from the above values. *, p < 0.01; **, p < 0.001.

**Fig. 3.** Gastrin mRNA levels following induction and de-induction. Antral mucosa was incubated in the presence of somatostatin antibodies, which resulted in a prompt increase in the concentration of gastrin mRNA. After maximum induction was achieved, [Leu]-D-Trp^28,Tyr^28]somatostatin-28 (STS ANALOGUE) was added to the incubation medium (arrow), which produced a prompt and steady de-induction of gastrin mRNA. Gastrin mRNA levels were measured by dot blot hybridization and are expressed in arbitrary units ± S.E.
Effects of Cycloheximide and Actinomycin D on Steady State Levels of Gastrin mRNA—The effects of cycloheximide, an inhibitor of protein synthesis, and actinomycin D, an agent that inhibits cellular biosynthesis at the gene transcriptional level, were examined by incubating antral mucosa under basal conditions, both with and without somatostatin immunoneutralization. Antral mucosal tissue was incubated in the presence or absence of somatostatin antibodies for 30 min, at which time either 5 μg/ml actinomycin D or 10 μg/ml cycloheximide were added to the medium. Antral mucosa was also incubated for 10 min with cycloheximide, at which time actinomycin D was added to the medium. After a 60-min incubation, the tissue were harvested and the concentration of gastrin mRNA measured by dot blot hybridization.

The addition of actinomycin D to the incubation medium decreased basal gastrin mRNA levels by 27.4 ± 8.5% (p < 0.02) (Fig. 5A) and attenuated the stimulatory effects of somatostatin immunoneutralization by 26.5 ± 8.0% (p < 0.02) (Fig. 5B). In response to incubation with cycloheximide, basal gastrin mRNA levels increased by 52.3 ± 8.4% (p < 0.01) (Fig. 5A); in contrast, no significant effect of cycloheximide on gastrin mRNA levels could be detected following antral somatostatin immunoneutralization (Fig. 5B). The addition of actinomycin D to the medium containing cycloheximide resulted in significant decreases in gastrin mRNA levels, both in the presence and absence of somatostatin antibodies (Fig. 5). No significant changes in the levels of cytoskeletal actin or ubiquitin mRNA were detected following the incubation of antral mucosa under any of the above conditions.

**DISCUSSION**

Somatostatin appears to play an important physiological role in modulating the release of a number of regulatory peptides in several different tissues (26). In addition to its location in the stomach and other digestive organs (27, 28), somatostatin-containing cells have been demonstrated in the endocrine pancreas (29), retina (30), cardiac vagus (31), and glomerulus of the kidney (32). As stated above, previous studies have supported the hypothesis that antral somatostatin exerts inhibitory effects on the gastrin cell by paracrine pathways, accomplished by release of the peptide from somatostatin cells into the immediate interstitial environment of the gastrin cell (6-8). Because of its universal distribution, the effects of somatostatin are likely vital to the biology of most organ systems. Therefore, the precise definition of its molecular mechanism of action would further enhance our understanding of its physiological importance.

Although the inhibitory effects of somatostatin on the release of several peptides, such as growth hormone, adrenocorticotropic, and thyroid-stimulating hormone, are well established (26), its effects on gene transcription and mRNA turnover have not been characterized previously. The present study represents the first report of the effect of somatostatin on the turnover of a specific mRNA. It would appear, therefore, that the effects of somatostatin on antral gastrin cells are multidimensional, whereby both pre- and posttranslational events are modulated. The capacity of other regulatory peptides to affect mRNA turnover has been observed earlier in other systems. Prolactin (33) and thyrotropin-releasing hormone (34) are known to stabilize casein mRNA and prolactin mRNA, respectively. In rat hepatoma cells, insulin has been shown to inhibit albumin mRNA at both the transcriptional and posttranscriptional levels (35). As in the present study, the molecular mechanisms by which these regulatory peptide motifs modulate mRNA turnover are not completely understood.

As depicted in Fig. 5, when antral mucosa was incubated under basal conditions in the presence of cycloheximide, gastrin mRNA levels increased by 52.3 ± 8.4%, while it had no effect when gastrin mRNA was stimulated by somatostatin immunoneutralization. Although an explanation for these observations cannot be offered unequivocally, these findings are consistent with superinduction, a cycloheximide-sensitive mechanism of mRNA degradation, in which gastrin mRNA is degraded by a selective, labile RNase (36). This RNase L system, which selectively degrades inducible mRNAs, has
been described in a number of other cells, including T lymphocytes and human monocytes, as well as in viruses (37, 38).

In the latter instance, the enzyme (2'-5')-A synthetase generates an obligatory co-factor during the synthesis of the labile RNase (39). Under the conditions of these experiments, somatostatin would produce its effects by stimulating the synthesis of the RNase, which in turn would selectively degrade gastrin mRNA. Although cycloheximide would also inhibit translation of gastrin mRNA, its predominant effect would be to inhibit the synthesis of the selective gastrin RNase, which would then induce an increase in the concentration of gastrin transcripts. Under the conditions in which endogenous somatostatin has been neutralized, RNase synthesis would not be stimulated, and maximum concentrations of gastrin mRNA are present in the cell. The enhancement of gastrin mRNA turnover. The addition of cycloheximide, under these conditions, would then permit the superinduction process to proceed. Another plausible explanation for these observations is that cycloheximide has stabilized gastrin mRNA by preservation of the polyosome structure. This possibility is, however, unlikely since no effect of cycloheximide was observed following the immunoneutralization of endogenous somatostatin.

The results of these studies indicate that the principal pretranslational effect of somatostatin on the antral gastrin cell is the enhancement of gastrin mRNA turnover. The precise biological relevance of its effect on gastrin gene transcription is difficult to ascertain with any degree of certainty. As illustrated in Fig. 2, the addition of 10^{-6} M somatostatin to the incubation medium did not significantly alter the rate of gastrin gene transcription under basal conditions. In contrast, following the immunoneutralization of endogenous antral somatostatin, a small (34%), but significant, increase in gastrin gene transcription was observed. In addition, somatostatin nearly abolished gastrin gene transcriptional activity that had been stimulated by either dbcAMP or carbachol (Fig. 2). These findings are consistent with several recent studies, including those by Godley and Brand (40), who transfected GH, pituitary cells with constructs containing the first exon of the human gastrin gene and the 5' regulatory sequence ligated upstream of the reporter gene chloramphenicol acetyltransferase. They showed that although no effect on basal promoter activity could be detected, the somatostatin analogue octreotide effectively antagonized chloramphenicol acetyltransferase activity stimulated by various regulatory peptides (40). Using antral mucosal explants, Harty et al. (3) demonstrated only a 34% decrease in basal gastrin release cultured in the presence of 10^{-6} M somatostatin; in contrast somatostatin nearly abolished carbachol-stimulated gastrin release. In experiments employing the same concentration of somatostatin, although Park et al. (41) detected no effect on unstimulated cells, somatostatin produced a 31% decrease in the uptake of [14C]aminopyrine by isolated parietal cells that had been stimulated by histamine. These observations (3, 40, 41) corroborate the results of the present studies and indicate that the inhibitory effects of somatostatin may be most physiologically relevant during stimulated, rather than basal, conditions. They also support the hypothesis that somatostatin exerts a local tonic restraint on various intracellular events, including gastrin gene transcription, and that its removal by immunoneutralization results in the stimulation of gastrin cell function.

Although the cellular mechanism of action of somatostatin has not been investigated thoroughly, current theories suggest that somatostatin may exert its effects by binding to a cell surface receptor that is coupled to N_{i}, the inhibitory guanine nucleotide binding protein (42). After activation of this inhibitory subunit by somatostatin, the accumulation of cyclic AMP is decreased, which not only directly suppresses cellular function, but may also indirectly inhibit the cell by blocking the accumulation of cytosolic calcium (43). The role of these second messengers in exerting the inhibitory effects of somatostatin on gastrin gene expression has not been evaluated. Further studies using homogeneous populations of cells, rather than intact antral mucosa, are warranted and should prove invaluable in helping to further our understanding of the precise cellular mechanism of action of somatostatin on the gastrin cell. In conclusion, the results of the present experiments indicate that somatostatin significantly decreases the rate of antral gastrin biosynthesis. Although the studies demonstrate an inhibitory effect of somatostatin on gastrin gene transcription, its predominant effect appears to involve the enhancement of gastrin mRNA turnover.

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