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Catecholamines Inhibit Gastric Epithelial [RGM-1] Cell Proliferation via Beta Adrenoceptors

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Summary: Catecholamines have been implicated in the modulation of normal cell growth, exerting inhibitory or excitatory control depending on the cell type. However, there is a dearth of information on the role of adrenergic mediators in gastric cell proliferation. In the present study, the effects of adrenaline (ADR) and noradrenaline (NOR) on mucosal cell growth and the cell cycle were evaluated in vitro using a normal rat gastric mucosal cell line RGM-1. Cell proliferation was assessed using [3H]-thymidine incorporation and cell cycle patterns were determined by DNA labeling with propidium iodide and flow cytometric quantification. The expressions of adrenoceptors in RGM-1 were determined by Western blot. ADR (0.01 – 10µM) and NOR (0.01 – 10µM) inhibited the growth of RGM-1 cells in a concentration-dependent manner. Pre-treatment of cells with ADR and NOR also inhibited the proliferation stimulated by epidermal growth factor (EGF). Neither phentolamine (non-selective α-adrenergic blocker), methoxamine (α1-selective agonist) nor clonidine (α2-selective agonist) significantly affected the inhibition of cell proliferation produced by ADR and NOR. Propranolol (non-selective β-adrenergic blocker) and butoxamine (selective β2-adrenergic blocker) significantly (but not totally) reversed the inhibitory action of ADR on cell proliferation. Furthermore, procaterol (selective beta-2 agonist) but not dobutamine (selective beta-1 agonist) had effects similar to those produced by ADR and NOR. Exposure of RGM-1 cells to both ADR and NOR caused significant inhibition of the G1 – S cycle progression as evidenced by the higher percentage of the G0/G1 phase and a decreased S-phase. This effect was blocked by pre-treatment with propranolol but not phentolamine. These results indicate that catecholamines inhibit the proliferation of RGM-1 cells probably partly through beta-2 receptors.

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Keywords: Cathecholamines; RGM-1; Cell proliferation; cell cycle; flow cytometry, [3H]-thymidine

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INTRODUCTION

The gastric fundic mucosa is regarded as a self-renewing epithelium, undergoing rapid cell proliferation in response to assaults from foods, drugs and an array of endogenous substances. It is estimated that the turn-over rate of the progenitor zone in the isthmus is about 33 – 40% per day (Karam and Leblond, 1993; Karam et al, 2003). The importance of the isthmal cell proliferation lies in the fact that by the process of migration and differentiation, they give rise to the functional cell lineages in the oxyntic mucosa such as the neck cells (for mucous secretion) and parietal cells (for acid secretion).

Several factors have been shown to be involved in the control of normal gastric epithelial cell proliferation. These include growth factors such as epidermal growth factor (Sasaki et al, 2003), transforming growth factor-alpha (TGF-α) (Chen et al, 1993)] and tumor necrosis factor-alpha (TNF-α) (Luo et al, 2005); hormones such as gastrin (Li and Hellander 1996), somatostatin (Lehy et al, 1979), erythropoietin (Itoh et al, 2006) and other endogenous peptides such as nitric oxide (Baatar et al, 2003) and prostaglandins (Sasaki et al, 2003).

Catecholamines have been implicated in the modulation of normal cell proliferation, exerting inhibitory or excitatory control depending on the cell type. Leicht et al (2003) observed that norepinephrine stimulated cardiac fibroblasts through the regulation of mitogen-activated protein kinase [MAPK]. Similarly, catecholamines stimulate proliferation of brown adipocytes (Thonberg et al, 2001), osteoblasts (Suzuki et al, 1998), proximal tubule cells (Cussac et al, 2002) as well as corneal epithelial cells (Jones and Marfurt, 1996). On the other hand, catecholamines inhibit the proliferation of lymphocytes (Sampere et al, 2004).

The effect of the adrenergic neurotransmitters on the gastrointestinal cell proliferation is also not
The progression of proliferating cells through the cell cycle is dependent upon the interplay of activities of cyclin-dependent kinases (cdk) and their regulatory subunits [cyclins] to enable cells to progress from G1 to S-phase (G1-S transition) and from G2 to M phase (G2-M transition) (Sherr and Roberts, 1995; 2004). The synthesis of appropriate cyclins during a specific phase is required for progression to take place. Therefore, the inhibition of a needed cyclin may result in the arrest of the cycle in a particular phase (Nakayama et al, 1996; Bartek and Lukas).

The aims of the present study are: to evaluate the capacity of two naturally occurring catecholamines to modulate gastric cell proliferation, to identify the adrenergic receptors involved in such activity, to assess the effects of the catecholamines on gastric epithelial cell cycle progression.

MATERIALS AND METHODS

Reagents:
Epinephrine (ADR), norepinephrine (NOR), propranolol (PRP), phenotolamine (PHENT), clonidine (CLON), methoxamine (METH), dobutamine (DOBUT), procaterol (PROCAT) and propidium iodide (PI) were all purchased from Sigma Chemical Co. (St. Louis, MO). A 1:1 mixture of Dulbecco's modified Eagle's medium and Ham's F-12 medium (DMEM/F12) was purchased from Life Technologies (Invitrogen catalog number 11320-033). Fetal Bovine Serum (FBS), Hank's Balance Salt Solution (HBSS) and Trypsin-EDTA were purchased from Gibco BRL (Grand Island, NY). Other reagents were of analytical grade and obtained from Sigma-Aldrich Inc (St. Louis, MO, USA), unless otherwise stated.

Cell culture:
Rat gastric mucosal epithelial cell line RGM-1 (RCB-0876, Riken Cell Bank, Tsukuba, Japan), a diploid, non-transformed epithelial line isolated from normal Wistar rat’s gastric mucosa (Kobayashi et al, 1996) was used for this study. The cells were grown in DMEM/F-12 medium containing 20% heat-inactivated, fetal bovine serum and supplemented with 100U/ml penicillin G, 100 μg/ml streptomycin, and 20% FBS in an incubator at 37°C, 95% humidity, and 5% CO2. Cells were routinely subcultured in 15ml medium in Iwaki flasks using trypsin/EDTA. Cultures were examined regularly under an inverted light microscope to monitor growth and rule out contamination. For this study, data for passages 9 – 22 were found to be consistent and were thus used.

Assessment of RGM-1 cell membrane integrity:
The degree of cellular necrosis in RGM-1 cells was estimated by measuring the level of lactate dehydrogenase (LDH) released into the culture media. RGM-1 cells were seeded to a subconfluent density of 4 x104 cells/well in 24-well plates (IWAKI Inc, Japan) and incubated overnight in DMEM F-12 supplemented with 20% FBS for adherence. The cells were then exposed to catecholamines at 10-fold dilutions ranging from 0.001 μM to 10 μM. Control cells were incubated with DMEM F12 only (negative control) or DMEM + 1% Triton X (positive control). Incubation was performed for 24h in triplicate. At the end of each incubation, culture medium was centrifuged at 250 x g for 5 minutes and 100μL aliquot was transferred to a clean 96-well Iwaki plate. The amount of LDH released into the culture media was quantified using a commercial kit (LDH-Cytotoxic Test; Wako, Osaka, Japan).

Cell Proliferation::
Basal and Epidermal Growth Factor (EGF) stimulated proliferative responses of cultured rat gastric epithelial cells RGM-1 to catecholamines were determined by [3H]-thymidine incorporation. Briefly, RGM-1 cells were seeded in 24-well culture plates at ~5x104 cells/ml and were allowed to grow in DMEM/F-12 medium containing 20% FBS for 24 h. Afterwards, cells were growth arrested in serum-free medium overnight and then treated with ADR or NOR [0.1μM – 10μM] in the presence or absence of inhibitors for 6, 12, 18 and 24 hr. In experiments involving the evaluation of adrenergic agonist/antagonist interactions, antagonists were added to the culture medium 45 minutes prior to the agonists. Five hours prior to final analysis, the cells were further incubated with [3H]-thymidine (0.5 μCi/ml).

After washing each well with ice-cold Normal Saline and detaching the cells from culture plates, the radioactivity of each sample was measured using a liquid scintillation counter (LS-6500, Beckman Instruments, Inc., Pullerton, CA).
The effect of catecholamines on the distribution of cell cycle phases was determined by flow cytometry using a Beckman-Coulter FACScan. Cells were plated at 5 × 105 cells in 60mm diameter plates in 2 ml of DMEM-F12 medium supplemented with 20% FBS. After reaching about 50% confluence, the cells were synchronized in the G0 phase by incubation in a serum-free medium for 48h. The cells were then treated with ADR or NOR in the presence or absence of adrenergic inhibitors. After 24h of incubation, cells were harvested and washed with PBS, resuspended in 500 μl of PBS, and fixed in 500 μl of ice-cold absolute ethanol at −20 °C. After incubation for 30 min, cell pellets were collected by centrifugation, resuspended in 0.5 ml of PBS containing 100 μg/ml RNase, and incubated at 37 °C for 30 min.

Then 0.5 ml of propidium iodide (PI) solution (50 μg/ml in PBS) was added, and the mixture was allowed to stain on ice for 60 min. The cells were analyzed with FACScan flow cytometer (Becton Dickinson, USA). For each experiment, a total of 104 cells were counted.

Analysis of the flow cytometry result was done using Cychred and WinMDI (Purdue University) software.

**Western blot analysis:**
RGM-1 cells were seeded in 100-mm plates at a density of 5 x 106. Cells were harvested by cell scraping, collected by centrifugation, and the pellet was washed once with PBS and then lysed in a lysis buffer composed of Mg2+- and Ca2+- free phosphate-buffered saline (PBS) supplemented with 20 mM Tris-HCl, pH 8.0, 1% NP40, 150 mM NaCl, 1 mM EDTA, 10% glycerol, 0.1% β-mercaptoethanol, 0.5 mM dithiothreitol, and a mixture of proteinase inhibitors consisting of 1 mM phenylmethylsulfonyl fluoride, 10 mg/ml aprotonin, 5 mg/ml leupeptin, 5 mM benzamidine, 1 mg/ml pepstatin, 2 mg/ml antipain hydrochloride (Boehringer, Mannheim, Germany), 50 mM 4-[2-aminoethyl]-benzenesulfonyl fluoride hydrochloride (Wako Pure Chemical Industries Ltd., Osaka, Japan) and 2 mM sodium orthovanadate (Sigma-Aldrich). The lysate containing 15 μg protein was electrophoresed in a 10-20% gradient SDS-PAGE mini gel (Dai-ichi Kagaku, Tokyo, Japan) and blotted onto a PVDF membrane using Multiphor II (Amersham Pharmacia Biotech, Buckinghamshire, UK) for 30 min. The blotted membrane was blocked with 5% skim milk in 10 mM Tris-HCl, pH 7.2, containing 150 mM NaCl and 0.5% Tween 20 and incubated with primary antibodies (0.1-1 mg/ml) described below at 4°C for 16 h. The membrane was then incubated with alkaline phosphatase-conjugated secondary antibodies (0.02 mg/ml), described below, for 4 h at room temperature. The membrane was rinsed, treated with nitroblue tetrazolium (Sigma-Aldrich) and 5-bromo-4- chloro-3-indolyl phosphate (Sigma-Aldrich) to visualize protein bands. The primary antibodies used were mouse anti-human monoclonal antibody against β1 and β2 adrenergic receptors (Transduction Laboratories, San Diego, CA, USA) and goat polyclonal antibodies against human actin (Santa Cruz Biotechnology, Santa Cruz, CA, USA). The secondary antibodies used were anti-mouse and anti-goat IgGs conjugated with alkaline phosphatase (Santa Cruz). The intensity of each band was imaged and the bands were observed to ascertain the presence of beta adrenoceptors on RGM-1 cells.

**Statistical analysis**
The data are presented as the mean ± SEM of each experimental point. One-way ANOVA was used to compare data between 3 or more groups. Differences among groups were examined using the Student's t-test when the F value was significant. Values are expressed as mean standard error of the mean [SEM] while the level of significance was set at P < 0.05.

**RESULTS**

**Cytotoxicity studies**
To select the non-cytotoxic concentrations of the catecholamines for the experiment, the release of lactate dehydrogenase (LDH) from RGM-1 cells in response to different concentrations of catecholamines was determined. As shown in Fig. 1, LDH release by RGM-1 cells was not significantly altered by catecholamine concentrations up to 10μM. However, significant increases in LDH release were observed at concentrations of 100μM and above. For the subsequent studies therefore, a concentration range of 0.01μM to 10μM was used. The positive control 1% Triton X-100 markedly increased LDH release for more than 2 folds.

**Proliferation studies**

a. **Effects of catecholamines on unstimulated proliferation of RGM-1 cells**
As shown in Fig. 2, exposure of RGM-1 cells to graded concentrations of ADR and NOR [0.01 – 10μM] for 12, 18 and 24 h caused a time- and dose-dependent inhibition of DNA synthesis. For the 6 h culture, neither ADR nor NOR had any significant effect on RGM-1 cell proliferation at the doses tested. However, for the 18 h culture, cell proliferation was significantly inhibited at the two highest concentrations [P <0.05] without affecting cell viability. Maximal inhibition was however obtained after 24 h of exposure to ADR and NOR at concentrations of 0.01μM (P < 0.05), 0.1μM and 1.0

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μM (P < 0.001). Therefore a concentration of 1.0 μM at 24 h exposure time was used in subsequent mechanistic experiments. When compared with NOR, there was no significant differences in the inhibitory pattern of ADR.

b. Effects catecholamines on EGF-induced proliferation of RGM-1 cells
Exposure of cells to ADR and NOR for 24 h also dose-dependently inhibited proliferation induced by a known mitogen, epidermal growth factor.

As shown in Fig. 3, exposure of RGM-1 cells to EGF (0.1 ng/ml) increased [3H]-thymidine incorporation to 162.81±1.02% over the control value (P < 0.001). Pre-treatment of the cells with ADR before incubation with EGF significantly reduced this stimulation to 142.5± 5.47 at the 0.01 μM concentration and to 105.08 ± 4.54 for the 10 μM concentration (Fig 3a). Similar pattern was obtained for the noradrenaline experiment (Fig. 3b).

Fig. 1
LDH release in RGM-1 Cells treated with graded concentrations of Catecholamines. Each vertical bar represents Mean ± SEM of six experiments per treatment. Triton X served as positive control.

Fig. 2
Effects of adrenaline (a) and noradrenaline (b) on [3H]-thymidine incorporation into RGM-1 cell line. Approximately 4 x 10^5 RGM-1 cells were added to flat bottom 24-well plates. Data represent the means of three independent experiments and were compared using the two-tailed Student t-test. * P<0.05; ** P<0.005
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c. Effects of non-selective adrenoceptor antagonists on the inhibitory action of catecholamine on RGM-1 cell proliferation

Exposure of RGM-1 cells to 1.0 μM the non-selective alpha adrenergic antagonist, phentolamine, prior to ADR treatment did not significantly affect the inhibitory activity of ADR on cell proliferation (Fig. 4a).

However, when the cells were exposed to similar concentrations of propranolol, a non-selective beta adrenergic antagonist prior to ADR treatment, there was a significant change in the inhibitory action of ADR on cell proliferation from 75.17 ± 2.53% [for ADR alone] to 94.22 ± 3.43% [for ADR + PRP]. Fig. 4b.

d. Effects of selective beta-adrenoceptor antagonists on the inhibitory action of catecholamine on RGM-1 cell proliferation

Based on the results from the experiments in (c) above, we investigated the role of specific beta adrenoceptor blocking drugs atenolol (β1) and butoxamine (β2) on the inhibitory action of ADR.

The results are presented in Fig. 5. Exposure of the RGM-1 cells to atenolol or butoxamine alone did not have any significant effects on the incorporation of thymidine. Also, pre-treatment of cells with atenolol did not alter the inhibitory activity of ADR on thymidine incorporation. However, exposure of the cells to butoxamine before ADR significantly reversed the inhibitory action of ADR to levels comparable to the control values.
Effects of pre-treatment with Phentolamine (a) and propranolol (b) on adrenaline-induced inhibition of RGM-1 cell proliferation. *P< 0.05; NS Not significant (Compared with control values)

e. Effects of selective adrenergic agonists on the proliferation of RGM-1 cells

To further confirm the involvement of adrenoceptors on the actions of ADR and NOR, the effects of selective agonists of the adrenoceptors on RGM-1 cell proliferation were investigated. Neither methoxamine (alpha-1 selective agonist) nor clonidine (alpha-2 selective agonist) significantly affected RGM-1 cell proliferation to any significant level (Fig. 6a).

The effects of the selective beta-1 agonist, dobutamine and beta-2 agonist, procaterol on cell proliferation are also shown in Fig. 4b. While dobutamine did not alter thymidine incorporation significantly at the dose tested, procaterol produced significant inhibition (Fig. 6b).
**Cell cycle studies**

The effects of ADR and NOR on the cell cycle of RGM-1 were determined by flow cytometry. As shown in Fig.7a & b, ADR caused accumulation of cells in the G0-G1 phase population cell cycle. In the control cells, the G0-G1 phase population was 60.13 ± 1.70% of the total cell population. The G0-G1 phase in the 0-1μM ADR and 0.1 μM NOR treated cells were 71.20 ± 1.39% (P < 0.05) and 68.13 ± 0.96% (P < 0.05) respectively.

Furthermore, the population of cells in the S-phase of the cells of cycle was significantly decreased by catecholamine treatment reducing to 30.07 ± 2.31 (P < 0.05) and 25.00 ± 1.13% in cells pre-exposed to 0.1 μM ADR and 0.1 μM NA respectively.

Fig 8 shows the effect of pre-treatment of RGM-1 cells with phentolamine (alphaadrenoceptor blocker) and propranolol (beta-adrenoceptor) blocker on cell cycle distribution. Phentolamine did not significantly reverse the effects of ADR on the G0-G1 phase (71.20 ± 1.39%) for ADR c.f. 69.43 ± 2.05% for ADR+PHENT. On the other hand, the propranolol significantly reversed the effects of ADR (71.20 ± 1.39% for ADR cf. 63.8 ± 1.9% for ADR+PROP). These results suggest that the accumulation of G0-G1 phase cells induced by catecholamine treatment may be mediated via the beta-adrenoceptor mechanism.

![Graph showing effects of selective β₁-adrenoceptor (atenolol) and β₂-adrenoceptor (butoxamine) antagonists on [3H]-thymidine incorporation into RGM-1 cell line. Approximately 4 x 10⁵ RGM-1 cells were added to flat bottom 24-well plates. Data represent the means of three independent experiments and were compared using the two-tailed Student t-test. * P<0.05, NSNot significant (Compared with control values).]
Catecholamines and gastric cell proliferation

In the present study, we have demonstrated that catecholamines caused inhibition of cell proliferation in the rat gastric mucosal cell lines in a dose-dependent manner. Results from the study also suggest that the observed effects of catecholamine on cell proliferation are evoked by beta-2 adrenoceptors, as suggested by the inhibitory activity of the non-selective beta-adrenergic antagonist, propranolol and the selective beta-2 adrenergic antagonist, butoxamine. Western blot analysis also indicated the presence of beta-2 adrenoceptors in RGM-1 cells. The implication of the present result is discussed based on the known gastrointestinal processes affected directly or indirectly by changes in cell proliferation.

Growth factors have been shown to play important roles in the maintenance of gastrointestinal tissue integrity, repair of gastrointestinal mucosal injury as well as ulcer healing. Such actions are particularly well documented for epidermal growth factor (EGF) (Basson et al, 1992; Tarnawski et al, 1995; Majumdar et al, 1996). This is corroborated in the present study in which EGF dose-dependently increased thymidine incorporation into RGM-1 cells. It is significant to note that both ADR and NOR produced greater inhibition of EGF-stimulated response than the basal state. It is therefore possible that a major locus of the inhibitory action of the catecholamines is the EGF-stimulatory pathways.

The integrity of the gastric mucosa is maintained by the interplay of anti-proliferative forces such as the number of apoptotic cells and the pro-proliferative forces. When the kinetic balance is tilted towards cell proliferation excessive growth of the gastric mucosa cells occur. A number of proliferation promoting substance, such as ethanol (Ge et al, 2007; Hernandez –Munoz et al, 2000) and Helicobacter pylori (Eslick et al, 1999) have been shown to predispose the stomach to chronic gastritis (Lynch et al, 1995; Cahill et al, 1996) and even gastric cancer (Parsonnet et al, 1991; Honda et al, 1998; Kamada et al, 1995).

In the present study, the proliferative effect of the potent mitogen, EGF was significantly inhibited by adrenaline and noradrenaline. The action of catecholamine may thus be used to explain the formation of stress induced gastric ulcers. Stress induced ulcers have been produced in several models in experimental animals using catecholamines (Beraha, 1980; Man, 1981).

The inhibition of the activity of growth factors under stressful conditions may explain in part the higher predisposition of the stomach wall to erosion. Cell proliferation is also important in ulcer healing process. It is known that failure of DNA synthesis characterize intractable ulcers (Kobayashi et al, 1998). The repair process in gastric mucosa injury involves an initial reconstitution of the epithelial surface via cell migration from gastric pits and glands (Svanes, 1982) and later by increased cell proliferation to replace lost cells (Silen et al, 1987; Tarnawski et al, 2000). Previous reports show that though EGF is produced in the salivary glands under normal conditions, it is also secreted at ulcer margins, causing not only migration, but also rapid proliferation of cells (Konturek et al, 1990). The high expression of EGF at ulcer margins was reported by Ma et al (Ma et al, 2000). EGF has also been shown to play significant roles in the healing of stress-induced ulcers (Konturek et al, 2000).
Fig. 7.
The distribution of cell cycle in Adrenaline (ADR) treated RGM-1 cells (A) and Noradrenaline (NA) treated cells (B). The distribution of cell cycle was assessed by flow cytometry. The data shown are the mean ± SEM three independent experiments, each with triplicate wells. The asterisk indicates a significant difference between control and treated cells, (P< 0.05). NS = Not significant (c.f. control)
Following our observation that the catecholamine inhibits gastric cell proliferation, we investigated the biochemical aspects of the signaling mechanism that may be responsible for this action. When the functional analyses of the adrenergic receptors involved were carried out, it was observed that most of the inhibitory actions of catecholamine were contributed by the β2 adrenoceptors. A number of studies have shown that the adrenoceptors are involved in modulating cell proliferation in a number of cells in the gastrointestinal tract. For example, catecholamines have been reported to stimulate proliferation of the intestinal epithelium through activation of 2 adrenoceptors located on crypt cells (Schaak et al, 2000) whereas catecholamines inhibit cell proliferation in the buccal epithelium of rat via β2 adrenoceptors (McInnes and Tutton, 1976). Although the actions of adrenaline and noradrenaline on cell proliferation was inhibited by the β2 adrenoceptor blocker, the possibility of the involvement of other beta adrenoceptor subtypes not investigated in this study should not be ruled out.

Thus further investigations into the role β3 adrenoceptors in gastric epithelial cell proliferation may be necessary. It may be concluded from this study that catecholamines inhibit the proliferation of gastric mucosal cells. In addition, beta adrenoceptor subtypes are involved, at least in part, in this process.

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