http://www.ncbi.nlm.nih.gov/pubmed/17921324

Am J Physiol Heart Circ Physiol. 2007 Dec;293(6):H3356-65. Epub 2007 Oct 5.

IL-17 stimulates MMP-1 expression in primary human cardiac fibroblasts via p38 MAPK- and ERK1/2-dependent C/EBP-beta , NF-kappaB, and AP-1 activation.

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Matrix metalloproteinases (MMPs) degrade collagen and mediate tissue remodeling. The novel cytokine IL-17 is expressed during various inflammatory conditions and modulates MMP expression. We investigated the effect of IL-17 on MMP-1 expression in primary human cardiac fibroblasts (HCF) and delineated the signaling pathways involved. HCF were treated with recombinant human IL-17. MMP-1 expression was analyzed by Northern blotting, RT-quantitative PCR, Western blotting, and ELISA; transcriptional induction and transcription factor binding by EMSA, ELISA, and reporter assay; and p38 MAPK and ERK1/2 activation by protein kinase assays and Western blotting. Signal transduction pathways were investigated using pharmacological inhibitors, small interfering RNA (siRNA), and adenoviral dominant-negative expression vectors. IL-17 stimulated MMP-1 gene transcription, net mRNA levels, protein, and promoter-reporter activity in HCF. This response was blocked by IL-17 receptor-Fc chimera and IL-17 receptor antibodies, but not by IL-6, TNF-alpha, or IL-1beta antibodies. IL-17-stimulated type I collagenase activity was inhibited by the MMP inhibitor GM-6001 and by siRNA-mediated MMP-1 knockdown. IL-17 stimulated activator protein-1 [AP-1 (c-Fos, c-Jun, and Fra-1)], NF-kappaB (p50 and p65), and CCAAT enhancer-binding protein (C/EBP)-beta DNA binding and reporter gene activities, effects attenuated by antisense oligonucleotides, siRNA-mediated knockdown, or expression of dominant-negative signaling proteins. Inhibition of AP-1, NF-kappaB, or C/EBP activation attenuated IL-17-stimulated MMP-1 expression. IL-17 induced p38 MAPK and ERK1/2 activation, and inhibition by SB-203580 and PD-98059 blunted IL-17-mediated transcription factor activation and MMP-1 expression. Our data indicate that IL-17 induces MMP-1 in human cardiac fibroblasts directly via p38 MAPK- and ERK-dependent AP-1, NF-kappaB, and C/EBP-beta activation and suggest that IL-17 may play a critical role in myocardial remodeling.

Full free study available

http://www.ncbi.nlm.nih.gov/pubmed/18653993

J Antibiot (Tokyo). 2008 May;61(5):285-90.

Oxacyclododecindione, a novel inhibitor of IL-4 signaling from Exserohilum rostratum.

Erkel G, **Belahmer H**, **Serwe A**, **Anke T**, **Kunz H**, **Kolshorn H**, **Liermann J**, **Opatz T**.

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In a screening program for new metabolites from fungi inhibiting the IL-4 mediated signal transduction, a novel chlorinated macrocyclic lactone, designated as oxacyclododecindione, was isolated from fermentations of the imperfect fungus Exserohilum rostratum. The structure was determined by a combination of spectroscopic techniques. Oxacyclododecindione inhibits the IL-4 induced expression of the reporter gene secreted alkaline phosphatase (SEAP) in transiently transfected HepG2 cells with IC50 values of 20-25 ng/ml (54-67.5 nM). Studies on the mode of action of the compound revealed that the inhibition of the IL-4 dependent signaling pathway is caused by blocking the binding of the activated STAT6 transcription factors to the DNA binding site without inhibiting tyrosine phosphorylation. The compound has no antibacterial or antifungal activity.

http://www.ncbi.nlm.nih.gov/pubmed/10995751

J Biol Chem. 2001 Jan 5;276(1):287-97.

ERK1 and ERK2 activate CCAAAT/enhancer-binding protein-beta-dependent gene transcription in response to interferon-gamma.

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Interferons (IFNs) regulate the expression of a number of cellular genes by activating the JAK-STAT pathway. We have recently discovered that CCAAAT/enhancer-binding protein-beta (C/EBP-beta) induces gene transcription through a novel IFN response element called the gamma-IFN-activated transcriptional element (Roy, S. K., Wachira, S. J., Weihua, X., Hu, J., and Kalvakolanu, D. V. (2000) J. Biol. Chem. 275, 12626-12632. Here, we describe a new IFN-gamma-stimulated pathway that operates C/EBP-beta-regulated gene expression independent of JAK1. We show that ERKs are activated by IFN-gamma to stimulate C/EBP-beta-dependent expression. Sustained ERK activation directly correlated with C/EBP-beta-dependent gene expression in response to IFN-gamma. Mutant MKK1, its inhibitors, and mutant ERK suppressed IFN-gamma-stimulated gene induction through the gamma-IFN-activated transcriptional element. Ras and Raf activation was not required for this process. Furthermore, Raf-1 phosphorylation negatively correlated with its activity. Interestingly, C/EBP-beta-induced gene expression required STAT1, but not JAK1. A C/EBP-beta mutant lacking the ERK phosphorylation site failed to promote IFN-stimulated gene expression. Thus, our data link C/EBP-beta to IFN-gamma signaling through ERKs.

Full free study available

http://www.ncbi.nlm.nih.gov/pubmed/17311279

J Cell Physiol. 2007 Jun;211(3):759-70.

Interleukin-1beta induces MMP-9 expression via p42/p44 MAPK, p38 MAPK, JNK, and nuclear factor-kappaB signaling pathways in human tracheal smooth muscle cells.

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Matrix metalloproteinases (MMPs) are responsible for degradation of extracellular matrix and play important roles in cell migration, proliferation, and tissue remodeling related to airway inflammation. Interleukin-1beta (IL-1beta) has been shown to induce MMP-9 production in many cell types and contribute to airway inflammatory responses. However, the mechanisms underlying MMP-9 expression induced by IL-1beta in human tracheal smooth muscle cells (HTSMCs) remain unclear. Here, we investigated the roles of p42/p44 MAPK, p38 MAPK, JNK, and NF-kappaB pathways for IL-1beta-induced MMP-9 production in HTSMCs. IL-1beta induced production of MMP-9 protein and mRNA in a time- and concentration-dependent manner determined by zymographic, Western blotting, and RT-PCR analyses, which was attenuated by inhibitors of MEK1/2 (U0126), p38 MAPK (SB202190), JNK (SP600125), and NF-kappaB (helenalin), and transfection with dominant negative mutants of MEK1/2, p38 and JNK, respectively. IL-1beta-stimulated phosphorylation of p42/p44 MAPK, p38 MAPK, and JNK was attenuated by pretreatment with U0126, SB202190, SP600125, or transfection with these dominant negative mutants of MEK, ERK, p38 and JNK, respectively. Furthermore, IL-1beta-stimulated translocation of NF-kappaB into the nucleus and degradation of IkappaB-alpha was blocked by helenalin. Finally, the reporter gene assay revealed that MAPKs and NF-kappaB are required for IL-1beta-induced MMP-9 luciferase activity in HTSMCs. MMP-9 promoter activity was enhanced by IL-1beta in HTSMCs transfected with MMP-9-Luc, which was inhibited by helenalin, U0126, SB202190, and SP600125. Taken together, the transcription factor NF-kappaB, p42/p44 MAPK, p38 MAPK, and JNK that are involved in MMP-9 expression in HTSMCs exposed to IL-1beta have now been identified.

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Bioorg Med Chem. 2007 Jan 15;15(2):1044-55. Epub 2006 Oct 27.

Synthesis and evaluation of 2-{[2-(4-hydroxyphenyl)-ethyl]amino}pyrimidine-5-carboxamide derivatives as novel STAT6 inhibitors.

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The STAT6 (signal transducers and activators of transcription 6) protein is activated by interleukin (IL)-4 and IL-13, and plays an important role in T-helper cell 2 (Th2) differentiation. STAT6 might therefore be an excellent therapeutic target for various allergic conditions, including asthma and atopic diseases. We synthesized a series of 2-{[2-(4-hydroxyphenyl)ethyl]amino}pyrimidine-5-carboxamide derivatives and evaluated their STAT6 inhibitory activities. Among these compounds, 4-(benzylamino)-2-{[2-(3-chloro-4-hydroxyphenyl)ethyl]amino}pyrimidine-5-carboxamide (2t, AS1517499) showed potent STAT6 inhibition with an IC(50) value of 21 nM, and also inhibited IL-4-induced Th2 differentiation of mouse spleen T cells with an IC(50) value of 2.3 nM and without influencing T-helper cell 1 (Th1) differentiation induced by IL-12.

http://www.ncbi.nlm.nih.gov/pubmed/18534856

Bioorg Med Chem. 2008 Jul 1;16(13):6509-21. Epub 2008 May 17.

Identification of 4-benzylamino-2-[(4-morpholin-4-ylphenyl)amino]pyrimidine-5-carboxamide derivatives as potent and orally bioavailable STAT6 inhibitors.

Nagashima S, **Nagata H**, **Iwata M**, **Yokota M**, **Moritomo H**, **Orita M**, **Kuromitsu S**, **Koakutsu A**, **Ohga K**, **Takeuchi M**, **Ohta M**, **Tsukamoto S**.

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Signal transducers and activators of transcription 6 (STAT6) is a key regulator of the type 2 helper T (Th2) cell immune response and a potential therapeutic target for allergic diseases such as asthma and atopic diseases. To search for potent and orally bioavailable STAT6 inhibitors, we synthesized a series of 4-benzylaminopyrimidine-5-carboxamide derivatives and evaluated their STAT6 inhibitory activities. Among these compounds, 2-[(4-morpholin-4-ylphenyl)amino]-4-[(2,3,6-trifluorobenzyl)amino]pyrimidine-5-carboxamide (25y, YM-341619, AS1617612) showed potent STAT6 inhibition with an IC(50) of 0.70nM, and also inhibited Th2 differentiation in mouse spleen T cells induced by interleukin (IL)-4 with an IC(50) of 0.28 nM without affecting type 1 helper T (Th1) cell differentiation induced by IL-12. In addition, compound 25y showed an oral bioavailability of 25% in mouse.

http://www.ncbi.nlm.nih.gov/pubmed/19204326

Blood. 2009 Apr 9;113(15):3558-67. Epub 2009 Feb 9.

Structure of the AML1-ETO eTAFH domain-HEB peptide complex and its contribution to AML1-ETO activity.

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AML1-ETO is the chimeric protein product of the t(8;21) in acute myeloid leukemia. The ETO portion of the fusion protein includes the eTAFH domain, which is homologous to several TATA binding protein-associated factors (TAFs) and interacts with E proteins (E2A and HEB). It has been proposed that AML1-ETO-mediated silencing of E protein function might be important for t(8;21) leukemogenesis. Here, we determined the solution structure of a complex between the AML1-ETO eTAFH domain and an interacting peptide from HEB. On the basis of the structure, key residues in AML1-ETO for HEB association were mutated. These mutations do not impair the ability of AML1-ETO to enhance the clonogenic capacity of primary mouse bone marrow cells and do not eliminate its ability to repress proliferation or granulocyte differentiation. Therefore, the eTAFH-E protein interaction appears to contribute relatively little to the activity of AML1-ETO.

http://www.ncbi.nlm.nih.gov/pubmed/10627454

Blood. 2000 Jan 15;95(2):494-502.

Interleukin-4-induced transcriptional activation by stat6 involves multiple serine/threonine kinase pathways and serine phosphorylation of stat6.

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Stat6 transcription factor is a critical mediator of IL-4-specific gene responses. Tyrosine phosphorylation is required for nuclear localization and DNA binding of Stat6. The authors investigated whether Stat6-dependent transcriptional responses are regulated through IL-4-induced serine/threonine phosphorylation. In Ramos B cells, the serine/threonine kinase inhibitor H7 inhibited IL-4-induced expression of CD23. Treatment with H7 did not affect IL-4R-mediated immediate signaling events such as tyrosine phosphorylation of Jak1, Jak3, insulin receptor substrate (IRS)-1 and IRS-2, or tyrosine phosphorylation and DNA binding of Stat6. To analyze whether the H7-sensitive pathway was regulating Stat6-activated transcription, we used reporter constructs containing different IL-4 responsive elements. H7 abrogated Stat6-, as well as Stat5-, mediated reporter gene activation and partially reduced C/EBP-dependent reporter activity. By contrast, IL-4-induced transcription was not affected by wortmannin, an inhibitor of the phosphatidyl-inositol 3'-kinase pathway. Phospho-amino acid analysis and tryptic phosphopeptide maps revealed that IL-4 induced phosphorylation of Stat6 on serine and tyrosine residues in Ramos cells and in 32D cells lacking endogenous IRS proteins. However, H7 treatment did not inhibit the phosphorylation of Stat6. Instead, H7 inhibited the IL-4-induced phosphorylation of RNA polymerase II. These results indicate that Stat6-induced transcription is dependent on phosphorylation events mediated by H7-sensitive kinase(s) but that it also involves serine phosphorylation of Stat6 by an H7-insensitive kinase independent of the IRS pathway.

(Blood. 2000;95:494-502)

Full free study available

http://www.ncbi.nlm.nih.gov/pubmed/12161424

J Biol Chem. 2002 Oct 11;277(41):38254-61. Epub 2002 Aug 2.

p38 Mitogen-activated protein kinase regulates interleukin-4-induced gene expression by stimulating STAT6-mediated transcription.

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STAT6 functions as a critical mediator of IL-4-stimulated gene activation, and the function of STAT6 is regulated by both tyrosine and serine kinase activities. Here we analyzed the role of serine phosphorylation in regulation of STAT6-mediated transcription. Optimal transcriptional response of IL-4-inducible promoters requires costimulatory signals through CD40-stimulated intracellular kinases such as p38 MAPK. We found that the p38 MAPK inhibitor SB202190 as well as the dominant negative p38 MAPK inhibited interleukin (IL)-4 regulated expression of CD23 in Ramos B cells. IL-4 stimulation did not stimulate p38 MAPK activity, but inhibition of p38 MAPK activity directly correlated with inhibition of IL-4-induced gene activation. Dissection of individual response elements on IL-4-regulated promoter showed that C/EBP beta-mediated transcription was insensitive to SB202190 treatment in B cells whereas STAT6-mediated transcription was regulated by p38 MAPK. The IL-4-induced immediate activation events of STAT6 were not affected by p38 MAPK activity. Furthermore, phosphoamino acid analysis and phosphopeptide mapping indicated that STAT6 is not a direct substrate for p38 MAPK. Instead, p38 MAPK was found to directly regulate the activity of the transactivation domain of STAT6. These results show that, in addition to the well established proinflammatory effects, p38 MAPK also provides a costimulatory signal for IL-4-induced gene responses by directly stimulating the transcriptional activation of STAT6.

Full free study available

http://www.ncbi.nlm.nih.gov/pubmed/18342537

Cytokine. 2008 Apr;42(1):39-47. Epub 2008 Mar 14.

IL-4-induced Stat6 activities affect apoptosis and gene expression in breast cancer cells.

Zhang WJ, **Li BH**, **Yang XZ**, **Li PD**, **Yuan Q**, **Liu XH**, **Xu SB**, **Zhang Y**, **Yuan J**, **Gerhard GS**, **Masker KK**, **Dong C**, **Koltun WA**, **Chorney MJ**.

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IL-4-induced Stat6 signaling is active in a variety of cell types, including immune cells and cancer cells, and plays an important role in the regulation of gene expression. Using EMSA gel shift assay and an antibody to Stat6, we phenotyped two breast cancer cell lines, ZR-75-1 being active Stat6(high) phenotype and BT-20 being defective Stat6(null) phenotype, respectively. Breast cancer cells carrying Stat6(null) phenotype exhibited increased spontaneous apoptosis compared with those carrying Stat6(high) phenotype. Expression microarray analyses demonstrated that IL-4 upregulated CCL26, SOCS1, CISH, EGLN3, and SIDT1, and downregulated DUSP1, FOS, and FOSB, respectively, in these breast cancer cells. Among those genes, CCL26 and SOCS1 were known genes regulated by IL-4/Stat6 pathway, but CISH, EGLN3, SIDT1, DUSP1, FOS, and FOSB were novel genes demonstrated to be IL-4 responsive for the first time. IL-4 also upregulated 38 genes unique to Stat6(null) BT-20 cells and 23 genes unique to Stat6(high) ZR-75-1 cells, respectively. Furthermore, Stat6(high) and Stat6(null) cells showed very different profiles of constitutively expressed genes relevant to apoptosis and metastasis among others, which serve as a valuable expression database and warrant for detailed studies of IL-4/Stat6 pathway in breast cancer.

http://www.ncbi.nlm.nih.gov/pubmed/16620708

Zhonghua Yi Xue Za Zhi. 2006 Jan 10;86(2):76-81.

[Impact of STAT6 signaling pathway blockade on apoptosis of human colon cancer cells]

[Article in Chinese]

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OBJECTIVE: To investigate the relationship between the signal transducer and activator of transcription 6 (STAT6) and human colon cancer.

METHODS: Four STAT6-specific recombinant plasmid vectors, pshRNA-STAT6-1, 2, 3, and 4 were constructed and transfected into the cultured human colon cancer cells of the line HT-29. Seventy-two hours later RT-PCR was used to detect the mRNA expression of STAT6 and the apoptosis-related genes Bcl-2 and Bax, flow cytometry (FCM) was used to detect the protein expression of phopho-STAT6 (pSTAT6). HT-29 cells were inoculated into a plate and transfected with pshRNA-STAT6-1 or pshRNA-STAT6-4, and HT-29 cells without transfection were used as controls. Seventy-two hours later FCM was used to observe the cell apoptosis. Another HT-29 cells were inoculated into a plate and transfected with pshRNA-STAT6-1 or pshRNA-STAT6-4, or blank liposome as controls. Seventy-two hours later. Western blotting was used to detect the protein expression of Bcl-2 and Bax genes.

RESULTS: The p-STAT6 protein expression rate was 3.2% +/- 0.6% in the pshRNA-STAT6-1 group, significantly lower than that of the blank control group (18.2% +/- 0.9%, $P < 0.01$) with an inhibition rate of 82.4%, and was 7.9% +/- 0.4% in the pshRNA-STAT6-4 group, significantly lower than that in the blank control group too ($P < 0.01$) with an inhibition rate of 56.6%. And the p-STAT6 protein expression rates of the pshRNA-STAT6-2 and pshRNA-STAT6-3 groups were 16.6% +/- 0.5% and 17.1% +/- 0.7% respectively, both not significant different from that of the blank control group (both $P > 0.05$). The early cell apoptosis rates of the pshRNA-STAT6-1 and pshRNA-STAT6-4 groups were 13.0% and 8.8% respectively, both significantly higher than that of the blank control group (0.4%, both $P < 0.05$). The mRNA expression of Bcl-2 was significantly lower and the mRNA expression of Bax was significantly higher in the pshRNA-STAT6-1 and pshRNA-STAT6-4 groups than in the blank control and blank liposome groups (all $P < 0.01$). The protein expression patterns of Bcl-2 and Bax was consistent with that of their protein expression.

CONCLUSION: STAT6 signaling pathway inhibits the apoptosis of colon cancer cells by regulation of the Bcl-2 and Bax genes.

http://www.ncbi.nlm.nih.gov/pubmed/16732981

Chin Med J (Engl). 2006 May 20;119(10):801-8.

Apoptosis induced by short hairpin RNA-mediated STAT6 gene silencing in human colon cancer cells.

Zhang MS, **Zhou YF**, **Zhang WJ**, **Zhang XL**, **Pan Q**, **Ji XM**, **Luo ZG**, **Wu JP**.

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BACKGROUND: The relationship between signal transduction and tumors has become one of the foci in cancer research. Signal transducer and activator of the transcription 6 (STAT6) signaling pathway is found to be activated in some cancer cells. But the function of the pathway in cancer cells is unknown. This study was undertaken to investigate the effect of the Stat6 signaling pathway on apoptosis in human colon cancer cells (HT-29 cells) and the possible mechanism of Stat6 by RNA interference techniques.

METHODS: Four eukaryotic expression plasmid vectors of short hairpin RNA (shRNA) specific for the STAT6 gene were designed and generated by molecular biological technology. The plasmid vectors were transfected into HT-29 cells by cation liposomes to block the Stat6 signaling pathway. The expressions of STAT6 mRNA and phosph-Stat6 protein were detected by the reverse transcriptase polymerase chain reaction (RT-PCR) method and flow cytometry respectively to screen the most effective shRNA at 72 hours after transfection. The apoptosis condition of the cells in which the expression of the STAT6 gene had been interfered was analyzed by flow cytometry and confocal microscopy. Both mRNA and protein expression of B cell lymphoma-2 (Bcl-2) and Bax were detected by RT-PCR and western blotting.

RESULTS: Two effective eukaryotic expression plasmid vectors of shRNA specific for the STAT6 gene were generated successfully. One can reduce the expression of the STAT6 gene by 82.4% and the other by 56.8% ($P < 0.01$). The apoptotic rate of colon cancer cells in which STAT6 gene expression had been interfered was significantly higher than that in controlled colon cancer cells ($P < 0.01$). In the cells in which the Stat6 signaling pathway was blocked, the levels of mRNA and protein Bcl-2 were significantly decreased, whereas those of Bax were significantly increased ($P < 0.01$).

CONCLUSIONS: The Stat6 signaling pathway can inhibit apoptosis in human colon cancer cells. The subsequent disorder of Bcl-2/Bax expression may play an important part in that process. The STAT6 gene may serve as a potential target in cancer therapy.

Full free study available

http://www.ncbi.nlm.nih.gov/pubmed/12847266

J Immunol. 2003 Jul 15;171(2):948-54.

Dependence of IL-4, IL-13, and nematode-induced alterations in murine small intestinal smooth muscle contractility on Stat6 and enteric nerves.

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IL-4 and IL-13 promote gastrointestinal worm expulsion in part through effects on nonlymphoid cells, such as intestinal smooth muscle cells. The roles of Stat6 in IL-4-, IL-13-, and parasitic nematode-induced effects on small intestinal smooth muscle contractility were investigated in BALB/c wild-type and Stat6-deficient mice treated with a long-lasting formulation of recombinant mouse IL-4 (IL-4C) or IL-13 for 7 days. Separate groups of BALB/c mice were infected with Nippostrongylus brasiliensis or were drug-cured of an initial Heligmosomoides polygyrus infection and later reinfected. Infected mice were studied 9 and 12 days after inoculation, respectively. Segments of jejunum were suspended in an organ bath, and responses to nerve stimulation and to acetylcholine and substance P in the presence and absence of tetradotoxin, a neurotoxin, were determined. Both IL-4 and IL-13 increased smooth muscle responses to nerve stimulation in wild-type mice, but the effects were greater in IL-13-treated mice and were absent in IL-13-treated Stat6-deficient mice. Similarly, hypercontractile responses to nerve stimulation in H. polygyrus- and N. brasiliensis-infected mice were dependent in part on Stat6. IL-13, H. polygyrus, and N. brasiliensis, but not IL-4, also increased contractility to acetylcholine by mechanisms that involved Stat6 and enteric nerves. These studies demonstrate that both IL-4 and IL-13 promote intestinal smooth muscle contractility, but by different mechanisms. Differences in these effects correlate with differences in the relative importance of these cytokines in the expulsion of enteric nematode parasites.

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Ph. Hug remark :
Look this interesting full study about responses to nerve stimulation.
EFS (1–20 Hz, 80 V, 1 ms) evoked a frequency-dependent contraction of longitudinal smooth muscle from small intestine (Fig. 1). The frequency and voltage of EFS were based on the results of preliminary experiments that established the optimum frequencies and voltage necessary to induce contractions that were mediated entirely by nerves rather than through a direct effect on smooth muscle .