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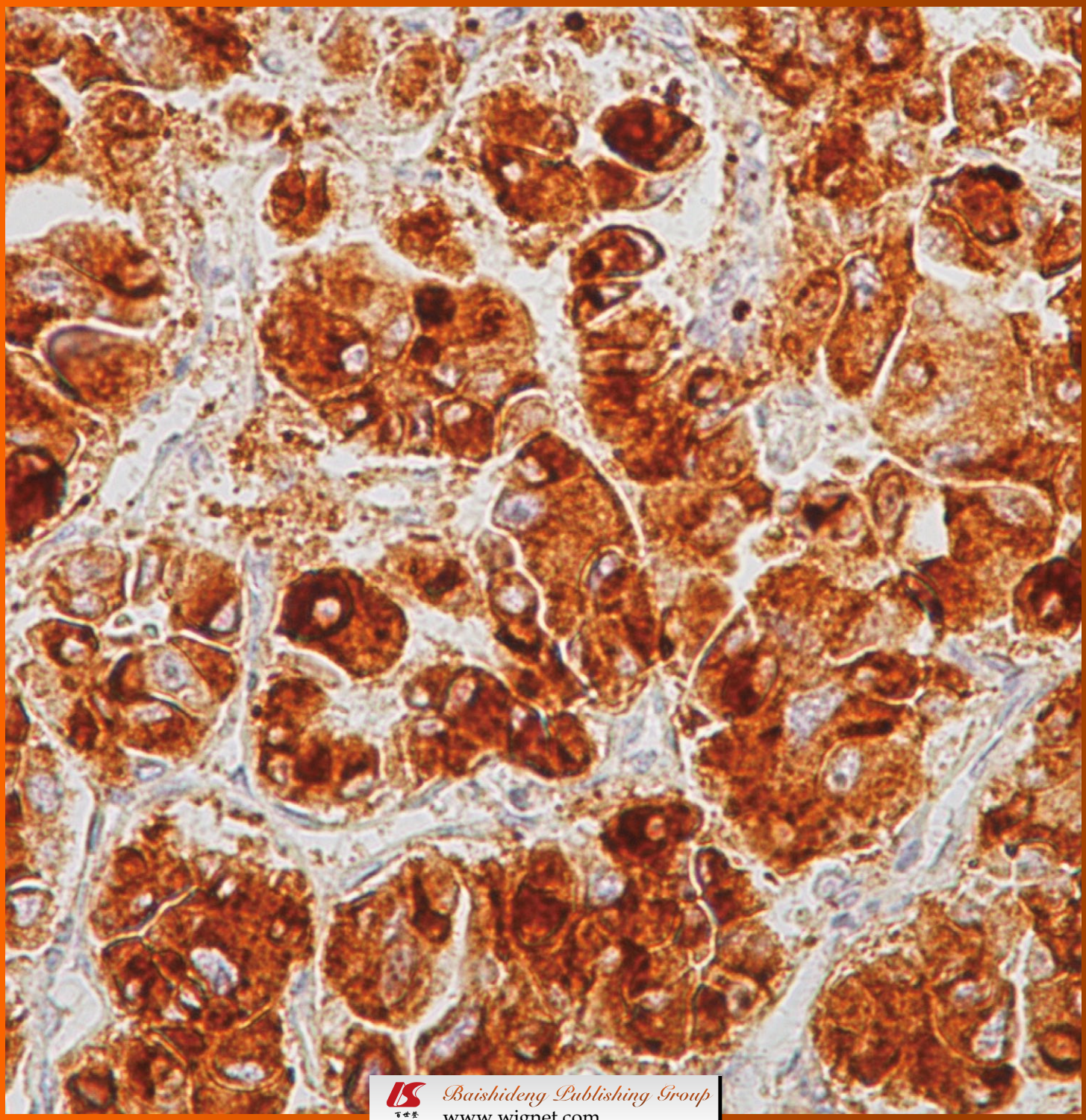

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EDITORIAL

MAPKs represent novel therapeutic targets for gastrointestinal motility disorders

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Abstract

The number of patients suffering from symptoms associated with gastrointestinal (GI) motility disorders is on the rise. GI motility disorders are accompanied by alteration of gastrointestinal smooth muscle functions. Currently available drugs, which can directly affect gastrointestinal smooth muscle and restore altered smooth muscle contractility to normal, are not satisfactory for treating patients with GI motility disorders. We have recently shown that ERK1/2 and p38MAPK signaling pathways play an important role in the contractile response not only of normal intestinal smooth muscle but also of inflamed intestinal smooth muscle. Here we discuss the possibility that ERK1/2 and p38MAPK signaling pathways represent ideal targets for generation of novel therapeutics for patients with GI motility disorders.

Key words: Mitogen-activated protein kinase; P38MAPK; ERK1/2; Smooth muscle; Contractile dysfunction

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INTRODUCTION

Several systems, including the central and enteric neural nexuses, interstitial cells of Cajal and smooth muscles provide coordinated regulation of gastrointestinal (GI) motility. The GI smooth muscle itself plays an important role; it contributes to general health and wellness when functioning normally but is also associated with morbidity and mortality when dysfunctional[1-4]. Alterations in GI motility with resultant changes in transit can contribute to abdominal pain, intestinal cramping, diarrhea, constipation and urgency to defecate. In overt inflammatory conditions of the bowel, such as infectious colitis, Crohn's disease and ulcerative colitis (i.e., inflammatory bowel disease, IBD), there have been longstanding observations of altered motility and impaired function of the intestinal smooth muscle[5-8]. Even functional GI disorders including non-erosive gastro-esophageal reflux disease (NERD), functional dyspepsia and idiopathic motility dysfunction (now classified under the panoptic irritable bowel syndrome,) seem to be associated with transformations in the contractile nature of smooth muscle[9-12].

Accumulated evidence suggests that the delicate balan-

ce between microbes, particularly commensal flora, and host defensive responses at the mucosal barrier have a pivotal role in the pathogenesis of chronic intestinal inflammation. The motility apparatus of the GI tract can act as an extension of the mucosal immune system, contributing to the evacuation of the luminal contents and to mucosal defense against noxious stimuli[13]. Motility dysfunction can secondarily induce abnormal growth of the intestinal flora, and the resulting disturbance of the flora can further aggravate mucosal inflammation[14]. This, in turn, would exacerbate intestinal dysmotility. Thus, motility disorders that arise in the context of inflammation or immune activation are clinically important as they can lead to systemic disease. Furthermore, defects in smooth muscle function are associated with the development of toxic megacolon. This condition is characterized by marked dilation of the distal colon and can occur with severe ulcerative colitis[15], in Hirschsprung's disease[16] and with infectious colitis[17].

In summary, GI motor disorders are reflective of a variety of important disease manifestations of varying etiologies. However, a central mechanistic feature of all these conditions is an alteration in the contractile processes that occur at the level of the GI smooth muscle. Therefore, it is very reasonable to target the molecular events underlying smooth muscle impairment. Although several drugs, including antimuscarinic agents, acetylcholine-releasing drugs, 5-HT_3 antagonists, 5-HT_4 agonists and dopamine D_2 antagonists, are currently used in clinical practice for GI motility disorders, antimuscarinic agents are the only ones that directly affect smooth muscle. In this regard, there is pressure for new pharmacologic agents capable of directly targeting GI smooth muscle for the restoration of normal smooth muscle contractility in the treatment of motility disorders. Recently, we have demonstrated that the extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (p38MAPK) signaling pathways play important roles in the contractile responses of both normal intestinal smooth muscle and inflamed intestinal smooth muscle[18,19]. In this commentary, we discuss the possibility that MAPK signaling pathways represent ideal targets for generation of novel therapeutics for patients with GI motility disorders.

CONVENTIONAL MECHANISM OF SMOOTH MUSCLE CONTRACTION

GI smooth muscle possesses distinct properties that distinguish it from other types of visceral and vascular smooth muscle[20]. Smooth muscle of the proximal stomach and sphincters exhibits sustained tone, whereas smooth muscle of the distal stomach, small intestine and colon exhibits variable (phasic) tone on which are superimposed rhythmic contractions. Cycles (slow-waves) of membrane depolarization and repolarization originate in pacemaker cells (i.e., interstitial cells of Cajal) and are transmitted to the smooth muscle cells (SMCs). The depolarization of SMCs primarily reflects activation of voltage-gated Ca^{2+} channels, resulting in Ca^{2+} entry from the extracellular space.

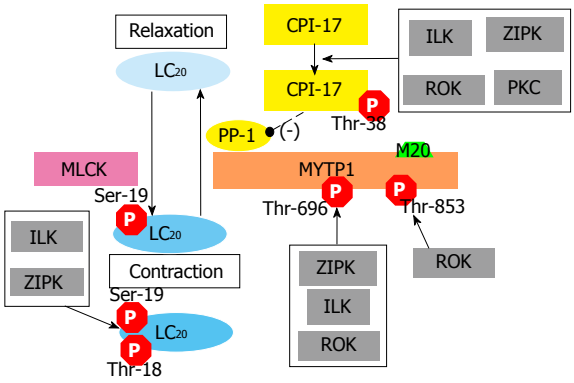

Figure 1 Conventional mechanisms of smooth muscle contraction. Smooth muscle contraction is primarily governed by the phosphorylation of the regulatory light chain (LC_{20}) of myosin II which is in turn driven by the balance between protein kinases responsible for phosphorylation of LC_{20} and protein phosphatases responsible for its dephosphorylation. Ca^{2+} sensitization of contractile force can result from the direct phosphorylation of LC_{20} by Ca^{2+}-independent protein kinases and/or inhibition of myosin phosphatase activity by Ca^{2+}-independent protein kinases. CPI-17: protein kinase C-potentiated inhibitory protein for protein phosphatase 1 of 17 kDa; ILK: integrin-linked kinase; LC_{20}: 20 kDa myosin light chain; MLCK: myosin light chain kinase; MYPT1: myosin targeting subunit 1 of myosin light chain phosphatase; M20: a 20 kDa non-catalytic subunit of myosin light chain phosphatase; PKC: protein kinase C; PP-1: catalytic subunit of protein phosphatase type-1; ROK: Rho-activated protein kinase; ZIPK: zipper-interacting protein kinase.

Concurrent stimulation of rhythmic smooth muscle by excitatory neurotransmitters elicits further depolarization and Ca^{2+} entry and activates intracellular signaling cascades that result in Ca^{2+} release from intracellular stores.

Although increased intracellular Ca^{2+} concentration ($[Ca^{2+}]$) is the paramount signal to initiate smooth muscle contraction, the contractile properties of the SMC are primarily governed by the phosphorylation of the regulatory light chain (LC_{20}) of myosin II[21,22] (Figure 1), which is itself driven by the balance between protein kinases responsible for phosphorylation of LC_{20} and protein phosphatases responsible for its dephosphorylation. To initiate contraction, increases in $[Ca^{2+}]$ activate myosin light chain kinase (MLCK), a Ca^{2+}/calmodulin-dependent enzyme[23]. MLCK phosphorylates LC_{20} on Ser-19, resulting in contraction of smooth muscle through increases in myosin ATPase activity and cross-bridge cycling. Smooth muscle myosin light chain phosphatase (MLCP) is responsible for the dephosphorylation of LC_{20}, resulting in relaxation of smooth muscle[24]. It is the balance between MLCK and MLCP activities that dictates the contractile activity of smooth muscle.

Although the Ca^{2+}/calmodulin/MLCK pathway plays a crucial role in phosphorylation of LC_{20}, the contraction of many smooth muscle tissues has frequently been observed in the absence of increased $[Ca^{2+}]$ in response to a variety of stimuli, a process commonly referred to as Ca^{2+} sensitization[22]. Currently, two mechanisms have been proposed to contribute to this phenomenon: (1) the direct phosphorylation of LC_{20} by Ca^{2+}-independent protein kinases and (2) inhibition of MLCP activity by Ca^{2+}-independent protein kinases. Both integrin-linked kinase (ILK)[25] and zipper-interacting protein kinase (ZIPK)[26,27]

can phosphorylate LC_{20} independently of Ca^{2+}/calmodulin. MLCP functions independently of Ca^{2+}/calmodulin and is regulated by G protein-coupled signaling pathways. Inhibition of MLCP results in greater LC_{20} phosphorylation and greater force development at given $[Ca^{2+}]$[22]. MLCP activity is regulated directly by phosphorylation of the myosin targeting subunit of MLCP (MYPT1)[24] and/or indirectly *via* phosphorylation of a protein kinase C (PKC)-potentiated phosphatase inhibitor protein of 17 kDa (CPI-17)[28]. It has been shown that phosphorylation of MYPT1 at Thr-696 (numbering for human sequence) by Rho-associated kinase (ROK)[29], ILK[30] and ZIPK[31] is associated with inhibition of MLCP activity. In contrast, ROK alone is thought to phosphorylate MYPT1 at Thr-853[32], also inhibiting MLCP activity. Alternatively, when CPI-17 is phosphorylated at the regulatory Thr-38 site, it becomes a potent inhibitor of MLCP. Although PKC was the original regulator upstream of CPI-17[28], other protein kinases including ILK[33], ZIPK[34] and ROK[35] have also been demonstrated to phosphorylate CPI-17 at Thr-38.

During intestinal inflammation, it is thought that the smooth muscle undergoes a phenotypic change whereby normal rhythmic contractions are supplanted by sustained Ca^{2+}-independent contractions that persist long after the mucosal response to injury has subsided. It will, therefore, be important to address how different protein kinase networks contribute to Ca^{2+} sensitization of intestinal smooth muscle contraction. Thus, the study of underlying mechanisms for the regulation of GI smooth muscle contractility will be important for our understanding of the basis for the loss of functional intestinal efficiency that characterizes the inflammatory bowel diseases and other intestinal motility disorders.

CONTRIBUTION OF ERK1/2 AND P38MAPK SIGNALING PATHWAYS TO CONTRACTILE RESPONSE IN NORMAL INTESTINAL SMOOTH MUSCLE

In addition to the protein kinases described above, accumulated evidence has shown that ERK1/2 and p38MAPK can also contribute to smooth muscle contraction[18,36-41]. We have recently examined the relative contributions of ROK, ERK1/2, p38MAPK and PKC to carbachol (CCh)-induced contraction of intestinal smooth muscle. Briefly, the ERK1/2 inhibitor, PD98059, and the p38MAPK inhibitor, SB203580, inhibited CCh-induced contractions of both rat ileal (longitudinal) and colonic (circular) smooth muscles, by 45% and 30% respectively (data not published). Furthermore, GF109203x, a broad PKC inhibitor, had an inhibitory effect (30% inhibition) on CCh-induced contraction in rat colonic smooth muscle, the extent of which was as similar to those observed with PD98059 or SB203580. Interestingly, however, ROK inhibitors Y27632 and H1152 had no effect.

The Ca^{2+} sensitization process has been examined previously in studies of rat ileal (longitudinal) smooth muscle[18]. When microcystin, a type 1 and type 2A protein phosphatase inhibitor, is applied to permeabilized smooth muscle clamped at pCa 9 (i.e., 1 nmol/L), a sustained contraction is observed that cannot be attributed to MLCK. This Ca^{2+}-independent contraction is thought to result from unmasking of endogenous Ca^{2+}-independent protein kinase activities and induction of the Ca^{2+} sensitization phenomenon. Pretreatment with either PD98059 or SB-203580 inhibited the microcystin-induced contraction of β-escin permeabilized rat ileal smooth muscle strips[18], indicating that both ERK1/2 and p38MAPK were involved. Interestingly, these findings were not observed in rat caudal artery. The microcystininduced contraction at pCa 9 of β-escin permeabilized rat ileal or caudal smooth muscle strips was not affected by pretreatment with Y27632[18,42]. These results indicate that the ERK1/2 and p38MAPK signaling pathways work more extensively than ROK in regulation of smooth muscle contractility, although the effects vary between ileum and colon, and with different agonists[18].

CONTRIBUTION OF ERK1/2 AND P38MAPK TO CONTRACTILE RESPONSES IN INFLAMED INTESTINAL SMOOTH MUSCLE

The molecular events underlying the phenotypic responses of the intestine to pathological inflammation are reflected in diverse tissue types, including smooth muscle. We have identified that Ca^{2+}-independent signaling pathways can influence contractile properties of intestinal smooth muscle under inflammatory conditions. Both ERK1/2 and p38MAPK protein kinase pathways are contributors to intestinal hypercontractility under Th2-mediated inflammatory events[19]. Although a hypercontractile response to CCh was observed in Th2 cytokines-related colitis[43,44], it still remains to be determined what types of downstream signaling pathways are involved in generating this response. In our experiments, colitis was induced in BALB/c mice by providing 5% dextran sulfate sodium (DSS) in drinking water for 7 d. Contractile responses of colonic circular smooth muscle strips to 118 mmol/L K^+ and carbachol (CCh) were assessed[19]. DSS-induced Th2 colitis in BALB/c mice was indicated by increased IL-4 and IL-6, with no changes in Th1 cytokines. Animals exposed to DSS had increased CCh-induced contraction (3.5-fold) and CCh-induced Ca^{2+}-sensitization (2.2-fold) responses in intact and a-toxin permeabilized colonic smooth muscle, respectively. The contributions of ERK1/2 and p38MAPK to CCh-induced contractions were significantly increased during Th2 cytokines-related colitis. Alternatively Ca^{2+}-independent contraction induced by microcystin was potentiated (1.5-fold) in mice with Th2 cytokines-related colitis. Both ERK1/2 and p38MAPK were found to contribute to this potentiation. Since treatment with Y27632 did not affect either CCh-induced contraction or microcystin-induced, Ca^{2+}-independent contraction in DSS-treated mice, the contribution of ROK to hypercon-

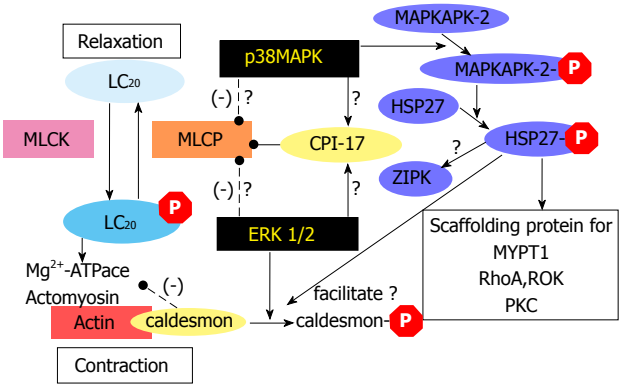

Figure 2 Proposed mechanisms by which ERK1/2 and p38MAPK signaling pathways contribute to smooth muscle contraction. MAPK pathways play important roles in modulating the contractile responses of normal and inflamed intestinal smooth muscles. MAPKs can alter the contractile activity of smooth muscle by (1) increasing the Mg^{2+}-ATPase activity of myosin Ⅱ, (2) phosphorylating caldesmon, a thin-filament associated protein, and promoting actin-myosin cross-bridges (3) phosphorylating HSP27 to reverse the inhibitory effects of caldesmon, or (4) directly regulating of myosin phosphatase activity. CPI-17: protein kinase C-potentiated inhibitory protein for protein phosphatase 1 of 17 kDa; ERK1/2: extracellular signal-regulated kinase 1/2; HSP27: phosphorylate heat shock protein; MAPKAPK-2: MAPK-activated protein kinase 2; LC_{20}: 20 kDa myosin light chain; MLCK: myosin light chain kinase; MLCP: myosin light chain phosphatase; p38MAPK: p38 mitogen-activated protein kinase; PKC: protein kinase C; ROK: Rho-activated protein kinase; ZIPK: zipper-interacting protein kinase.

tractility in inflamed colonic circular smooth muscle was determined to be negligible. We also have shown that the ERK1/2- and p38MAPK-associated hypercontractility is accompanied by significant increases in ERK1/2 and p38MAPK expression in the muscularis propria of colonic tissue from DSS-treated mice. Furthermore, we have examined the expression of ERK1/2 and p38MAPK in human colonic smooth muscle from patients with IBD[19] and found that their expression is also altered. Immunohistochemical analysis of total-ERK1/2 and total-p38MAPK was carried out on human colonic sections from non-IBD (normal) and IBD (Crohn's disease or ulcerative colitis) patients. Interestingly, the positive staining of total-ERK1/2 and p38MAPK in the muscularis propria was increased in sections from patients with ulcerative colitis, compared to Crohn's disease patients and non-IBD controls. These results are convincing since ulcerative colitis is thought to exhibit a Th2-like cytokine profile[45]. Taken together, these results indicate that murine Th2 colitis resulted in colonic smooth muscle hypercontractility with increased Ca^{2+}-sensitization. Both ERK1/2 and p38MAPK pathways contributed to this contractile dysfunction, and expression of these kinases was altered in patients with ulcerative colitis.

POSSIBLE MECHANISMS BY WHICH ERK1/2 AND P38MAPK CONTRIBUTE TO SMOOTH MUSCLE CONTRACTION

As described above, both the ERK1/2 and the p38MAPK pathways play important roles in contractile response, not only of normal intestinal smooth muscle but also of inflamed intestinal smooth muscle. Although it has yet to be determined precisely how ERK1/2 and p38MAPK signaling pathways contribute to smooth muscle contraction, the following mechanisms, as outlined in Figure 2, can be considered. In one scenario, ERK1/2 and p38MAPK activation can increase the Mg^{2+}-ATPase activity of myosin Ⅱ. ERK1/2 has been shown to phosphorylate caldesmon, a thin-filament associated protein that prevents the binding of myosin to actin[46]. The phosphorylation of caldesmon by ERK1/2 weakens the affinity of caldesmon toward actin[47], thereby promoting cross-bridge cycling and force development. Alternatively, p38MAPK has been shown to phosphorylate and activate MAPK-activated protein kinase 2 (MAPKAPK-2)[48], which can in turn phosphorylate heat shock protein (HSP) 27[49].Phosphorylated HSP27 is able to reverse the inhibitory effects of caldesmon on the Mg^{2+}-ATPase activity of myosin Ⅱ[46,50]. Another possible mechanism by which ERK1/2 and p38MAPK contribute to smooth muscle contraction is through regulation of MLCP activity, although this pathway has yet to be fully established. We have recently shown that both ERK1/2 and p38MAPK are involved in microcystin-induced contraction at pCa 9 in β-escin permeabilized rat ileal smooth muscle strips. Interestingly, increase in microcystin concentration from 1 μmol/L up to 10 μmol/L abolished the inhibitory effects of these ERK1/2 and p38MAPK pathways, suggesting that ERK1/2 and p38MAPK contribute to smooth muscle contraction *via* inhibition of MLCP activity[18]. We are currently further examining whether ERK1/2 and p38MAPK pathways are involved in MLCP regulation in intact intestinal smooth muscle and determining the underlying mechanisms.

MAPK INHIBITORS FOR ERK1/2 AND P38MAPK PATHWAYS AS POTENTIAL THERAPEUTIC TARGETS FOR DISEASES

ERK1/2 and p38MAPK are subfamilies of the MAPKs. In addition to ERK1/2 and p38MAPK, there are two other MAPKs; c-Jun NH2-terminal kinase (JNK1, 2 and 3) and ERK5[51]. ERK1/2 and p38MAPK are activated by a diverse range of stimuli including cytokines, growth factors and matrix proteins that bind to various receptor tyrosine kinases, G-protein coupled receptors, cytokine receptors, and integrins. Signals generated from these cell surface receptors initiate a cascade of signaling events that lead to downstream activation of the MAPKs. ERK1/2 and p38MAPK are activated by phosphorylation of specific Thr and Tyr residues by MAP-kinase kinases (MKK)[51]. MKK1 and MKK2 phosphorylate and activate ERK1 and ERK2, respectively[52], while MKK3 and MKK6 phosphorylate and activate p38MAPK[53]. It has been shown that the ERK1/2 signaling pathway is involved in cell differentiation and proliferation, programmed cell death, cell survival, cell motility and angiogenesis[54]. Alternatively, the p38MAPK signaling pathway plays an especially important role in the production of cytokines such as IL-1, tumor necrosis factor-α (TNF-α), and IL-6[55]. Therefore,

Table 1 MEK1/2 or p38MAPK inhibitors in ongoing clinical trials

Inhibitor	Sponsor	Phase	Study title	Status
MEK1/2 inhibiors				
AZD6244	AstraZeneca	Phase Ⅱ	Randomised study to compare the efficacy of AZD6244 *vs* TMZ	In progress
	National Cancer Centre, Singapore	Phase Ⅰ/Ⅱ	AZD6244 and sorafenib in advanced hepatocellular carcinoma	In progress
	University of Oxford	Phase Ⅱ	Docetaxel with or Without AZD6244 in melanoma (DOC-MEK)	In progress
	Massachusetts General Hospital	Phase Ⅱ	AZD6244 in cancers with BRAF mutations	In progress
	Other than listed above, almost 20 clinical trials are in progress.			
GDC0973	Genentech	Phase Ⅰ	A study of relative bioavailability and food effect study of GDC-0973 in healthy subjects	Completed
	Genentech	Phase Ⅰ	Study of GDC-0973/XL518 in patients with solid tumors	In progress
RDEA119	Ardea Biosciences, Inc	Phase Ⅰ/Ⅱ	RDEA119 and sorafenib combination dose escalation study	In progress
GSK1120212	GlaxoSmithKline	Phase Ⅰ	Investigate safty, pharmacokinetics and pharmacodynamics of GSK2118436 & GSK1120212	In progress
	GlaxoSmithKline	Phase Ⅰ	A study of the GSK MEK inhibitor GSK1120212 and everolimus in cancer subjects	In progress
	Other than listed above, 10 clinical trials are in progress.			
p38MAPK inhibitors				
VX-702	Vertex Pharmaceuticals Incorporated	Phase Ⅱ	A study in rheumatoid arthritis with an investigational oral p38MAP kinase inhibitor VX-702	Completed
	Vertex Pharmaceuticals Incorporated	Phase Ⅱ	Phase 2 clinical study in RA with an investigational oral p38 MAP kinase inhibitor VX-702	Completed

Information was obtained from ClinicalTrials.gov (http://clinicaltrials.gov/ct2/home)

the ERK1/2 signaling pathway contributes to various cell cycle-related diseases, including cardiovascular disease[56], cerebral vasospasm[57] and malignancies[58], whereas the p38MAPK signaling pathway is associated with inflammatory diseases including arthritis, psoriasis, IBD and asthma[55]. While PD98059 and SB203580 are classic inhibitors used in many in vitro studies of ERK1/2 and p38MAPK, respectively, several novel kinase inhibitors for ERK1/2 or p38MAPK have already seen use in clinical trials[59]. For example, the benzimidazole derivative, AZD6244, potent second generation inhibitor of MEK1/2, was recently studied in a phase I study to assess its safety, pharmacokinetics and pharmacodynamics in 57 patients with advanced cancer[60]. The 50 % maximal tolerated dose (100 mg BID) was well tolerated with skin rash being the most frequent and dose-limiting side effect. Most other adverse effects were of grade 1 or 2. A strong reduction in ERK1/2 phosphorylation was seen in tumor biopsies and nine patients showed disease stabilization lasting for at least 5 mo. Blocking of the ERK1/2 signaling pathway with MEK1/2 inhibitors (AZD6244, GDC0973, RDEA119, GSK1120212, etc.) has also evaluated in clinical trials for treatment of various malignancies, such as melanoma, breast cancer, colonic cancer, non-small cell lung cancer and a number of leukemias[59]. On the other hand, p38MAPK inhibition has been suggested to be potentially beneficial as a therapeutic strategy in inflammatory disease processes, and several different p38MAPK inhibitors have been tested in animal models of rheumatoid arthritis[61]. In each of these studies, p38MAPK inhibition was shown to reduce disease severity and maintain joint integrity with a reduction in the loss of cartilage and bone. Several p38MAPK inhibitors have advanced into clinical trials on treatment of rheumatoid arthritis in human subjects, although only a few have made it as far as phase Ⅱ. Unfortunately these compounds have poor safety profiles, including adverse effects in the central nervous system and liver[62] and, as a result, clinical research must move forward cautiously. Clinical trials on MEK1/2 inhibitors and p38MAPK inhibitors are summarized in Table 1.

ERK1/2 AND P38MAPK PATHWAYS ARE NEW POTENTIAL THERAPEUTIC TARGETS FOR PATIENTS WITH GI MOTILITY DISORDERS

As the ERK1/2 and p38MAPK signaling pathways are already being exploited for therapeutics development in a broad range of diseases (discussed above), they may also be possible new therapeutic targets for GI motility disorders that accompany gastrointestinal smooth muscle dysfunction. Patients suffering from symptoms associated with altered gastrointestinal motility experience decreased quality of life. Although several medications including anti-muscarinic agents, acetylcholine-releasing drugs, 5-HT_3 antagonists, 5-HT_4 agonists and dopamine D_2 antagonists are currently available in clinical practice for GI motility disorders, there are still cases where their therapeutic efficacy is not satisfactory. The ERK1/2 and p38MAPK signaling pathways play an important role in the contractile response not only of normal intestinal smooth muscle but also of inflamed intestinal smooth muscle. These pathways represent ideal targets for generation of novel therapeutics for patients with GI motility disorders. Since several kinase inhibitors for ERK1/2 or p38MAPK are already available

and used in clinical trials as described above, blockade of the ERK1/2 or p38MAPK signaling pathway with selective kinase inhibitors may be a good approach for developing new therapeutics for GI motility disorders.However, the potential toxicity of systemic ERK1/2 or p38MAPK inhibition, which may affect a multitude of growth factor signaling pathways that regulate cell proliferation and tissue homeostasis, will need to be addressed before new therapeutics can be developed. MEK1/2 inhibitors can be used in clinical trials only in several advanced, life-threatening cancers where there are no better therapeutic options. In these cases, the benefits of using MEK inhibitors for treatment could outweigh their side effects and toxicity. On risk-benefit considerations[59], currently available MEK1/2 inhibitors are not sufficiently beneficial and safe to be used in clinical trials in humans with GI motility disorders. Therefore, we eagerly await the next generations of ERK1/2 and p38MAPK signaling pathway inhibitors. These compounds, which may avoid systemic adverse effects because of greater specificity with reduced toxicity or smooth muscle tissue-selective delivery, could become a new therapeutic option for patients with GI motility disorders.

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CASE REPORT

Primary hepatic gastrinoma: Report of a case and review of literature

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Abstract

Primary hepatic gastrinoma is a very rare ectopic gastrinoma with less than 20 cases reported worldwide. We report the case of a patient with hypergastrinemia who was subjected to exhaustive preoperative and intraoperative imaging and also careful surgical exploration of the duodenum and pancreas which failed initially to identify the primary tumour. Eventually the patient was subjected to left liver lobectomy, as a small palpable lesion was noted intraoperatively. The diagnosis of gastrinoma requires a high index of clinical suspicion and the flawless cooperation of many specialties.

Key words: Primary hepatic gastrinoma; Zollinger-Ellison syndrome

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INTRODUCTION

Zollinger-ellison syndrome (ZES) was first described in 1955 as a constellation of findings, which included: refractory peptic ulceration, gastric acid hypersecretion, diarrhea, and a non-β islet cell tumor of the pancreas[1]. It was later confirmed that the islet cell tumor secreted peptide hormone gastrin and was the cause of ZES. The vast majority of gastrinomas are found in what has been referred to as the gastrinoma triangle. This is an imaginary anatomic region defined by the confluence of cystichepatic duct junction superiorly, the junction of the neck and body of pancreas medially and the junction of the 2nd and 3rd part of the duodenum inferiorly. Gastrinomas that arise away from this triangle are very rare[2,3].

We present the case of a 56 year old patient with hypergastrinemia who underwent exploratory laparotomy

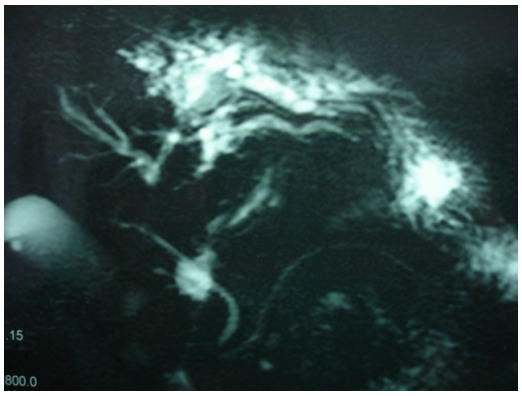

Figure 1 Magnetic resonance cholangiopancreatography revealing dilatation of left liver lobe biliary tree.

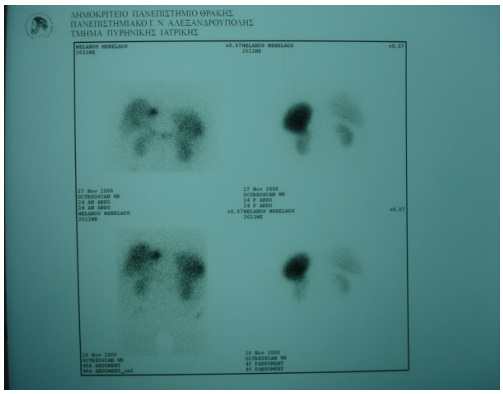

Figure 2 Octreoscan showing increased uptake close to the left liver lobe.

and curative resection for primary hepatic gastrinoma.

CASE REPORT

A 56-year-old male was referred because of a history of recurrent upper gastrointestinal haemorrhage and a high serum gastrin level. The patient had persistent heartburn and acid regurgitation for 16 years. Several oesophagogastroduodenoscopies (OGDs) revealed diffuse erosive oesophagitis and initially the presence of *Helicobacter pylori* (*H. pylori*). At the age of 46, after various eradication regimens against *H. pylori*, he was subjected to truncal vagotomy and Billroth Ⅱ gastrojejunostomy followed by long term prophylactic antisecretory treatment. At that time, gastrin levels were measured at 375 pg/mL (upper normal limit 80 pg/mL) and the Octreoscan test was negative for gastrinoma. Therefore, his hypergastrinemia was attributed to his antisecretory treatment. At the age of 52 he had the first episode of upper gastrointestinal bleeding. OGD indicated four anastomotic ulcers plus a bleeding duodenal ulcer with negative IgG antibodies against *H. pylori* and negative Campylobacter-like organism test. Three years later he had a new episode of upper gastrointestinal bleeding that necessitated transfusion of 4 blood units. Last year his gastrin levels were measured at 1688 pg/mL, which are pathognomonic of gastrinoma.

Abdominal ultrasonography (US) revealed hepatic steatosis and a hypoechoic lesion in the left liver lobe. No other abdominal pathological condition was found. A computed tomography (CT) scan of the abdomen showed intrahepatic dilatation of the biliary tree in the left liver lobe. No lesion was detected. Similarly, the magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) that followed (Figure 1) revealed dilatation of the left lobe biliary tree, but still no lesion was evident. The endoscopic ultrasound (EUS) did not reveal any tumor in the pancreas, duodenum or neighboring lymph nodes. The somatostatin receptor scintigraphy (SRS) using ^{111}In-DTPA-D-Phe^{1}-octreotide (Octreoscan®, Mallinckrodt, Petten, The Netherlands) indicated increased uptake of radiotracer close to the left liver lobe (Figure 2).

The patient underwent an exploratory laparotomy. We explored the gastrinoma triangle using intraoperative ultrasound (IOUS) and specimens from the head of the pancreas and from the neighboring lymph nodes were sent for frozen sectioning. All came back normal. However a small lesion (~1 cm) was palpable at the left liver lobe (segment Ⅲ) and therefore we performed a left lobectomy (segments Ⅱ and Ⅲ).

Pathological analysis showed compact groups of large neoplastic cells with granular eosinophilic cytoplasm and large atypical nuclei with inclusions. The cells were arranged in an insular pattern with angiofibrotic septa. (Figure 3A) Immunohistochemical (IHC) stains were positive for tumor markers such as chromogranin A (Figure 3B), cytokeratin (AE1-AE3), Neuron Specific Enolase (NSE), synaptophysin, gastrin (Figure 3C) and HepPar1. Proliferative activity was estimated with 15% Ki67-positive tumor cell nuclei (Figure 3D). The final diagnosis was a neuroendocrine tumor that fell in the gastrinoma category.

Twenty months postoperatively, the patient is asymptomatic and his blood gastrin levels remain within the normal range (19 pg/mL).

DISCUSSION

Gastrin-producing tumors are the most frequent pancreatic endocrine tumors, with an incidence of 0.5-1.5 new cases/10^6 people/yr[4] and are responsible for the ZES. More than 80% of gastrinomas are located in the gastrinoma triangle[5]. The vast majority of tumors are found in this pancreatic head-duodenal area, mainly in the duodenal submucosa (40%-50%), the head of the pancreas (30%-50%) or in the neighboring lymph nodes (19%)[2]. Ectopic gastrinomas are rare (< 5%) and have been reported in the stomach, ovaries, omentum, kidneys, lymph nodes, jejunum, esophagus, extrahepatic biliary tree, and liver[6-15]. The latter has been reported in fewer than 20 cases[16,17]. As the liver is a very common site of metastases from gastrinoma, the differential diagnosis of primary hepatic gastrinomas can be difficult. Primary hepatic

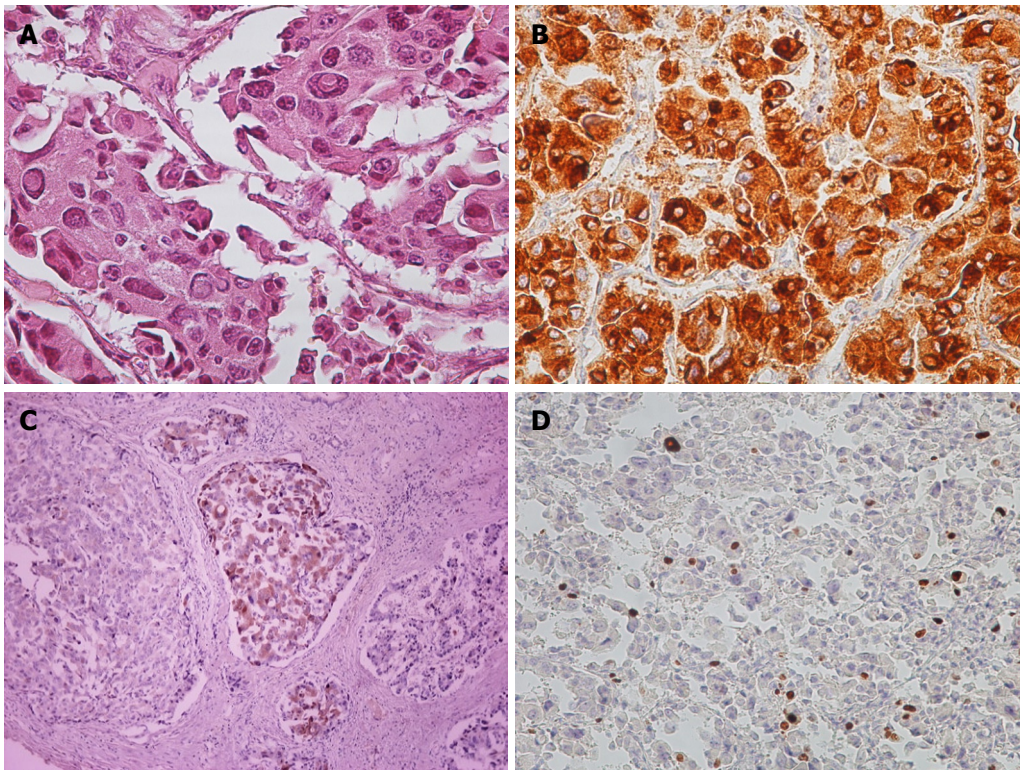

Figure 3 Pathological and immunohistochemical staining images. A: Hematoxylin and Eosin stain (×200); B: Chromogranin A+ (×200); C: Gastrin+ (×200); D: Ki67 15% (×200).

gastrinomas seem to occur in slightly younger patients compared to patients with other ZES tumors, show a predilection for male patients and have not been associated with multiple endocrine neoplasia type 1 (MEN-1)[18]. In approximately 75% of patients with ZES a single tumor (sporadic gastrinoma) is responsible for their symptoms, whereas in 25% of patients diagnosed with ZES, patients will have gastrinomas (often multiple) in the setting of the MEN-1 syndrome[6].

To make the diagnosis of gastrinoma a high index of suspicion is required. Findings may include recurrent *H. pylori*-negative peptic ulcers or peptic ulcers associated with complications (bleeding, perforation), chronic diarrhea, ulcers at a young age, family history of ulcers or MEN-1 syndrome[19].

Gastrinomas can have either a benign or malignant course, but even those that are malignant seem to be slow-growing tumors. Approximately 65% of gastrinomas are malignant and up to 30%-40% of patients will have evident metastatic disease at initial presentation. Malignancy cannot be established cytologically, but is determined by invasion of contiguous structures, the presence of vascular or lymphatic invasion, or most definitively by the presence of metastases at various locations, including lymph nodes, liver, and bone[6].

CT scan, MRI, and US are widely used during the initial evaluation and are excellent for visualization of larger tumors (> 1-2cm) and metastatic disease. OGD and EUS are often used to assess the upper gastrointestinal tract with pancreas and biliary tree. In recent years, the Octreoscan/SRS has successfully localized neuroendocrine tumors (primary or nodal metastases) in up to 78%-86% of cases, and is quickly becoming the imaging modality of choice for the diagnosis of patients with suspected gastrinomas[20]and, in our opinion, it should always be requested. Selective arterial secretin injection with hepatic vein sampling for gastrin, as described by Imamura *et al*[21], is helpful in regionalizing disease to the gastrinoma triangle or pancreatic body/tail, especially preoperatively[6]. However, imaging studies often detect regional nodal disease rather than the primary itself, although the location of regional disease can often lead the surgeon to the primary site (e.g. duodenum). The IOUS is a modality that can assist the surgeon to detect a small sized lesion, as current transducer resolution permits the detection of 2 mm lesions[22]. If preoperative imaging studies fail to detect any lesion, the use of IOUS should be seriously considered.

At the time of diagnosis our patient presented with symptoms suggestive of severe peptic ulcer disease due to gastric hyperacidity, along with extremely high serum levels of gastrin (> 1000 pg/mL), which are almost pathognomonic of the gastrinoma syndrome[23]. A careful search for MEN-1 was performed, as its presence would have changed the therapeutic approach. Exhaustive preoperative and intraoperative imaging and also careful surgical exploration of the duodenum and pancreas failed to identify the primary tumor.

Surgical resection is the treatment of choice and is the only chance for cure with a reported respectability rate up to 86% in the literature, and eugastrinemia in up to 60%

post-operatively, 40% at 5 years, and 34% at 10 years[24-26]. Norton *et al* recommend surgical exploration of all ZES patients with resectable and sporadic disease as it has been shown to increase overall disease-related survival[27]. Adjuvant therapy following complete resection (R0) provides no survival benefit. Orthotopic liver transplantation is an option when the locoregional disease is controlled[6,28].

Alternative therapies such as radiofrequency ablation, chemotherapy (doxorubicin, streptozocin, 5-fluorouracil), interferon, transplantation, and angiographic chemoembolization can be utilized, when there is no place for surgery due to diffuse disease or medical comorbidities[6,7,28,29,30]. Although chemotherapy can suppress progression of disease, gastrinomas can be resistant to conventional therapy with limited availability for second line treatment options. This has sparked interest in the use of molecular targeted therapy, utilizing VEGF, mTOR, and tyrosine kinase inhibitors[31,32]. Recently, treatment strategies include the use of peptide inhibitors that have been designed with a high affinity for receptors that may be overexpressed by neuroendocrine tumors. Radiolabeled somatostatin analogs (octreotide) are being employed for both imaging and radiotherapy[33].

In conclusion, primary hepatic gastrinomas are immensely rare. Diagnosis requires a high index of clinical suspicion and the flawless cooperation of many specialities including gastroenterologists, radiologists, surgeons and pathologists. The numbers are small and follow-up is limited. There is no standardized surgical approach when dealing with extrapancreatic extraintestinal gastrinomas. Surgical resection remains the only chance for cure.

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Purinergic signaling in the gastrointestinal tract

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Figure 1 Geoffrey Burnstock, PhD, DSc, FAA, FRCS(Hon), FRCP(Hon), FMedSci, FRS, Professor, Autonomic Neuroscience Centre, Royal Free and University College, Medical School, Rowland Hill Street, London NW3 2PF, United Kingdom.

Abstract

Geoffrey Burnstock completed a BSc at King's College London and a PhD at University College London. He held postdoctoral fellowships with Wilhelm Feldberg (National Institute for Medical Research), Edith Bülbring (University of Oxford) and C. Ladd Prosser (University of Illinois). He was appointed to a Senior Lectureship in Melbourne University in 1959 and became Professor and Chairman of Zoology in 1964. In 1975 he became Head of Department of Anatomy and Developmental Biology at UCL and Convenor of the Center of Neuroscience. He has been Director of the Autonomic Neuroscience Institute at the Royal Free Hospital School of Medicine since 1997. He was elected to the Australian Academy of Sciences in 1971, the Royal Society in 1986, the Academy of Medical Sciences in 1998 and an Honorary Fellow of the Royal College of Surgeons and the Royal College of Physicians in 1999 and 2000. He was awarded the Royal Society Gold Medal in 2000. He is editor-in-chief of the journals Autonomic Neuroscience and Purinergic Signalling and on the editorial boards of many other journals. Geoffrey Burnstock's major research interest has been autonomic neurotransmission and he is best known for his seminal discovery of purinergic transmission and receptors, their signaling pathways and functional relevance. He has supervised over 100 PhD and MD students and published over 1400 original papers, re-views and books. He was first in the Institute of Scientific Information list of most cited scientists in Pharmacology and Toxicology from 1994-2004 [59.083 citations (March 2011) and an h-index of 109].

Key words: Geoffrey Burnstock; Purinergic signaling; Gastrointestinal tract

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INTRODUCTION AND EDUCATIONAL EXPERIENCE

Geoffrey Burnstock (Figure 1) completed a BSc (Special) at King's College, University of London in 1953, then a PhD

from King's College and University College London, University of London (Supervisors: Professor JZ Young and Dr. Peggy Brown) in 1957. After moving to Melbourne in 1959, he was awarded an Honorary MSc from Melbourne University in 1962 and later a DSc in 1971. He was awarded an Honorary MRCP in London in 1987 and twelve years later an Honorary FRCS in England and in 2000, FRCP.

My educational background has been extremely multidisciplinary, starting with zoology, then anatomy and developmental biology, and then my most important contributions are probably in physiology and pharmacology and, most recently, in pathology.

ACADEMIC STRATEGIES AND ACADEMIC GOALS

My academic strategies and goals have been to develop different aspects of autonomic neuroscience, with particular emphasis on purinergic signaling[1]. In particular, I have tried to help bridge basic science, clinical medicine and the pharmaceutical industry.

ACADEMIC ACHIEVEMENTS

ATP was well established as an intracellular energy source involved in the Krebs cycle and other biochemical pathways, so our suggestion that it was also an extracellular signaling molecule in the early 1970s[2] was not widely accepted for the next 20 years. However, when the receptors for ATP were cloned and characterized in the early 1990s, purinergic signaling was recognized and is now a rapidly expanding field[3,4]. The initial studies describing purinergic neuromuscular transmission were carried out on the gut[5].

Non-adrenergic, non-cholinergic neuromuscular transmission

There was early recognition of atropine-resistant responses of the gastrointestinal tract to parasympathetic nerve stimulation. However, it was not until the early 1960s that autonomic transmission other than adrenergic and cholinergic was established. In 1963, electrical activity was recorded in the guinea-pig taenia coli using the sucrose-gap technique and, after stimulation of the intramural nerves in the presence of adrenergic and cholinergic blocking agents, an inhibitory hyperpolarizing potential was observed[6,7]. The hyperpolarizing responses were blocked by tetrodotoxin, a neurotoxin that prevents the action potential in nerves without affecting the excitability of smooth muscle cells, indicating their neurogenic nature and establishing them as inhibitory junction potentials in response to non-adrenergic, non-cholinergic (NANC) nerves. This work was extended by an analysis of the mechanical responses to NANC nerve stimulation of the taenia coli[8].

Purinergic signaling

The next step was to try to identify the transmitter released during NANC inhibitory transmission in the gut and by NANC excitatory transmission which we later identified in the urinary bladder. From the work of Jack Eccles and others, we knew that several criteria needed to be satisfied to establish a neurotransmitter: synthesis and storage in nerve terminals; release by a Ca^{2+}-dependent mechanism; mimicry of the nerve-mediated responses by the exogenously applied transmitter; inactivation by ectoenzymes and/or neuronal uptake; and parallel block or potentiation of responses to stimulation by nerves and exogenously applied transmitter. We examined many different substances in the late 1960s, including amino acids, monoamines and neuropeptides, but none satisfied the criteria. However, on reading the literature, I discovered a seminal paper by Drury and Szent-Györgyi[9] showing powerful extracellular actions of purines on heart and blood vessels, papers by Feldberg showing extracellular actions of ATP on autonomic ganglia and a paper by Pamela Holton in 1959[10], which showed release of ATP during antidromic stimulation of sensory nerves supplying the rabbit ear artery. So we tried ATP and to our surprise it beautifully satisfied all the criteria needed to establish it as a transmitter involved in NANC neurotransmission[5]. In 1972, I published an article in *Pharmacological Reviews* formulating the purinergic neurotransmission hypothesis[2]. My own view is that ATP, recognized as an early biological molecule, evolved both as an intracellular energy source and an extracellular signalling molecule.

Cotransmission

During a sabbatical leave visiting the laboratory of Che Su and John Bevan at UCLA, we were disconcerted to find ATP release, not only from NANC intrinsic inhibitory enteric neurons, but also for sympathetic nerves supplying the taenia coli[11]. However, this raised the question in my mind that ATP might be released as a cotransmitter from sympathetic nerves and after discovering many hints in the literature, I formulated the cotransmitter hypothesis in 1976 in a Commentary to *Neuroscience*[12], which unfortunately also raised controversy because of the widely held concept called 'Dales Principle' although actually defined by Eccles, that one nerve only releases one transmitter. The electrical recordings Mollie Holman and I made during sympathetic neurotransmission in the guinea-pig vas deferens in the early 1960s showed excitatory junction potentials (EJPs) in response to single pulses that summed and facilitated, until at a critical depolarization, a spike was generated leading to contraction. However, what was puzzling was that receptor antagonists to noradrenaline (NA) as the transmitter recognized at that time in sympathetic nerves did not block the EJPs, although bretylium, which prevents release of transmitter from sympathetic nerves, did reduce them. It was not until over 20 years later, when Peter Sneddon joined my laboratory in London, that we showed that α, β-methyleneATP, a slowly degradable analog of ATP that acts as a selective desensitizer of the ATP receptor[13], abolished the EJPs and spritzed ATP mimicked the EJP, but NA did not. Purinergic cotransmission is now well established, not only in

sympathetic nerves, but also in parasympathetic, sensory-motor and enteric nerves, and more recently ATP has been shown to be co-released with glutamate, GABA, dopamine, NA, 5-hydroxytryptamine and acetylcholine (ACh) in different populations of nerve fibers in the central nervous system[14].

Receptors to purines and pyrimidines

Implicit in purinergic transmission is the existence of specific receptors. In 1978, I proposed a basis for distinguishing two types of purinergic receptors, one selective to adenosine (called P1), which was antagonized by methylxanthines, and the other selective for ATP/ADP (called P2)[15]. A pharmacological basis for distinguishing two types of P2-purinoceptors, defined as P2X and P2Y, was proposed in 1985[16] and we were lucky that when P2 receptors were cloned in the early 1990s and second messenger mechanisms examined, this subclassification was consistent with P2X ion channel receptors and P2Y G protein-coupled receptors[17]. Currently 4 subtypes of P1 receptors are recognized, 7 subtypes of P2X receptors and 8 subtypes of P2Y receptors, including some responsive to the pyrimidines, UTP and UDP[18]. It was shown that three of the P2X receptor subunits combine to form cation pores either as homomultimers and heteromultimers, and more recently heterodimerization has been shown between P2Y receptor subtypes. Many non-neural as well as neuronal cells express multiple receptors[19] and this poses problems about how they mediate interacting physiological events. It is becoming clear that the purinergic signaling system has an early evolutionary basis with fascinating recent studies showing cloned receptors in two primitive invertebrates, *Dictyostelium* and *Schistosoma* that resemble mammalian P2X receptors.

Physiology of purinergic signaling

While early studies were largely focused on short-term signaling in such events as neurotransmission, neuromodulation, secretion, chemoattraction and acute inflammation, there has been increasing interest in long-term (trophic) signaling involving cell proliferation, differentiation, motility and death in development, regeneration, wound healing, restenosis, epithelial cell turnover, cancer and ageing. For example, in blood vessels there is dual short-term control of vascular tone by ATP released as an excitatory cotransmitter from perivascular sympathetic nerves to act on P2X receptors on smooth muscle, while ATP released from endothelial cells during changes in blood flow (shear stress) and hypoxia acts on P2X and P2Y receptors on endothelial cells leading to production of nitric oxide and relaxation[20]. In addition, there is long-term control of cell proliferation and differentiation, migration and death involved neovascularization, restenosis following angioplasty and atherosclerosis.

There is now abundant evidence for the widespread expression of purinoceptors in the gut involved in synaptic transmission and neuromodulation in the myenteric and submucous plexuses, in control of secretion, in peristaltic reflex activity and in mediation of colic pain[21-23].

Purinergic neuropathology and therapeutic potential

Primitive sprouting of central neurons was shown in experiments in which the enteric nervous system was transplanted into the striatum of the brain[24]. It was later shown that this was due to a growth factor, released from enteric glial cell acting synergistically with ATP, its breakdown product adenosine and nitric oxide. It is suggested that similar synergistic activity of purines and growth factors might be involved in stem cell activity.

It was established early that ATP was a major cotransmitter with ACh in parasympathetic nerves mediating contraction of the urinary bladder of rodents. In healthy human bladder, the role of ATP as a cotransmitter is minor. However, in pathological conditions, such as interstitial cystitis, outflow obstruction and most types of neurogenic bladder, the purinergic component is increased to about 40%. Similarly, in spontaneously hypertensive rats, there is a significantly greater cotransmitter role for ATP in sympathetic nerves.

$P2X_3$ receptors were cloned in 1995 and shown to be largely located in small nociceptive sensory nerves that label with isolectin B4[25,26]. Central projections are located in inner lamina 2 of the dorsal horn of the spinal cord and peripheral extensions in skin, tongue and visceral organs. A unifying purinergic hypothesis for the initiation of pain was published[27] and a hypothesis describing purinergic mechanosensory transduction in visceral organs in 1999[28], where ATP, released from lining epithelial cells during distension, acts on $P2X_3$ and $P2X_{2/3}$ receptors in subepithelial sensory nerve endings to send nociceptive messages *via* sensory ganglia to the pain centers in the brain. Supporting evidence including: epithelial release of ATP; immuno-localization of $P2X_3$ receptors on subepithelial nerves; and activity recorded in sensory nerves during distension that is mimicked by ATP and reduced by $P2X_3$ receptor antagonists, has been reported in the bladder, ureter and gut[29]. Purinergic mechanosensory transduction is also involved in urine voiding. There is also strong interest in the potential roles of purinergic signaling in trauma and ischemia, neurodegenerative conditions including Alzheimer's, Parkinson's and Huntington's diseases and in multiple sclerosis and amyotrophic lateral sclerosis.

CONCLUSION

Purinergic signaling is now widely accepted for its involvement in a wide spectrum of physiological and pathophysiological activities[3,30]. This was recognised by the Award for 'Lifetime Achievement in Digestive Sciences', the Janssen Award in Gastroenterology 2000, The Royal Society Gold Medal, 2000, the Copernicus Gold Medal, Ferrara, 2009, the British Neuroscience Annual Award for 'Outstanding Contributions to British Neuroscience' 2009 and the Gaddum Memorial Award of the British

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Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011 Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011, San Francisco, CA 94143, United States

January 27-28, 2011
Falk Workshop, Liver and Immunology, Medical University, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany

January 28-29, 2011
9. Gastro Forum München, Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference, Sydney, NSW, Australia

February 17-20, 2011
APASL 2011-The 21st Conference of the Asian Pacific Association for the Study of the Liver
Bangkok, Thailand

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation, Dublin, Ireland

February 24-26, 2011
International Colorectal Disease Symposium 2011, Hong Kong, China

February 26-March 1, 2011
Canadian Digestive Diseases Week, Westin Bayshore, Vancouver, British Columbia, Canada

March 03-05, 2011
42nd Annual Topics in Internal Medicine, Gainesville, FL 32614, United States

March 07-11, 2011
Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings, Sarasota, FL 34234, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011, Birmingham, England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011, Jacksonville, FL 34234, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research, Istanbul, Turkey

March 26-27, 2011
26th Annual New Treatments in Chronic Liver Disease, San Diego, CA 94143, United States

April 06-07, 2011
IBS-A Global Perspective, Pfister Hotel, 424 East Wisconsin Avenue, Milwaukee, WI 53202, United States

April 07-09, 2011
International and Interdisciplinary Conference Excellence in Female Surgery, Florence, Italy

April 20-23, 2011
9th International Gastric Cancer Congress, COEX, World Trade Center, Samseong-dong, Gangnam-gu, Seoul 135-731, South Korea

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition, Riyadh, Saudi Arabia

April 25-29, 2011
Neurology Updates for Primary Care, Sarasota, FL 34230-6947, United States

April 28-30, 2011
4th Central European Congress of Surgery, Budapest, Hungary

May 07-10, 2011
Digestive Disease Week, Chicago, IL 60446, United States

May 12-13, 2011
2nd National Conference Clinical Advances in Cystic Fibrosis, London, England, United Kingdom

May 19-22, 2011
1st World Congress on Controversies in the Management of Viral Hepatitis (C-Hep), Palau de Congressos de Catalunya, Av. Diagonal, 661-671 Barcelona 08028, Spain

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn, Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011, Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV
SPIGC, II ESYS, Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer, Barcelona, Spain

September 2-3, 2011 Falk Symposium 178, Diverticular Disease, A Fresh Approach to a Neglected Disease, Gürzenich Cologne, Martinstr. 29-37, 50667 Cologne, Germany

September 10-11, 2011
New Advances in Inflammatory Bowel Disease, La Jolla, CA 92093, United States

September 30-October 1, 2011
Falk Symposium 179, Revisiting IBD Management: Dogmas to be Challenged, Sheraton Brussels Hotel, Place Rogier 3, 1210 Brussels, Belgium

October 19-29, 2011
Cardiology & Gastroenterology
Tahiti 10 night CME Cruise, Papeete, French Polynesia

October 22-26, 2011
19th United European Gastroenterology Week, Stockholm, Sweden

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management, ANA Interconti Hotel, 1-12-33 Akasaka, Minato-ku, Tokyo 107-0052, Japan

December 01-04, 2011
2011 Advances in Inflammatory Bowel Diseases/Crohn's & Colitis Foundation's Clinical & Research Conference, Hollywood, FL 34234, United States

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GENERAL INFORMATION

World Journal of Gastrointestinal Pathophysiology (*World J Gastrointest Pathophysiol*, *WJGP*, online ISSN 2150-5330, DOI: 10.4291), is a bimonthly, open-access (OA), peer-reviewed journal supported by an editorial board of 296 experts in gastrointestinal pathophysiology from 39 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results.

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The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJGP* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJGP* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGP* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

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The major task of *WJGP* is to report rapidly the most recent results in basic and clinical research on gastrointestinal pathophysiology, including all aspects of normal or abnormal function of the gastrointestinal tract, hepatobiliary system, and pancreas. *WJGP* specifically covers growth and development, digestion, secretion, absorption, metabolism and motility relative to the gastrointestinal organs, as well as immune and inflammatory processes, and neural, endocrine and circulatory control mechanisms that affect these organs. This journal will also report new methods and techniques in gastrointestinal pathophysiological research.

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There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

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Key words

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Patholo gical changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

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The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyper tension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express t test as t (in italics), F test as F (in italics), chi square test as χ^2 (in Greek), related coefficient as r (in italics), degree of freedom as υ (in Greek), sample number as n (in italics), and probability as P (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1

mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc*. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2150-5330/g_info_20100107160355.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc*.
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc*.
Biology: *H. pylori*, *E coli*, *etc*.

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