Maturitas 105 (2017) 23–29

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Impact of chemotherapy on gastrointestinal functions and the enteric nervous system

Jonathan Escalante, Rachel M. McQuade, Vanesa Stojanovska, Kulmira Nurgali*

College of Health and Biomedicine, Victoria University, Western Centre for Health Research and Education, Sunshine Hospital, St Albans, VIC 3021, Australia

ARTICLE INFO

Keywords:
Enteric neuropathy
Chemotherapy
Chemotherapy-induced constipation
Chemotherapy-induced diarrhea

ABSTRACT

Chemotherapy is the main treatment for many cancers, including colorectal cancer, a type of cancer with some of the highest prevalence and mortality rates worldwide. Although chemotherapeutic drugs have greatly improved the survival rates of cancer patients, there are many side-effects associated with their use. The gastrointestinal side-effects of chemotherapy often lead to dose reduction or even discontinuation of treatment, which in turn affects the clinical outcome. Gastrointestinal side-effects, such as chemotherapy-induced diarrhea and constipation, may persist many years after treatment, greatly reducing quality of life. Current treatments for these side-effects have many adverse effects themselves; therefore, new approaches are needed to address this problem. Changes in the enteric nervous system located within the gastrointestinal tract and controlling its functions have been implicated in many disorders. Recent studies providing insight into the association between chemotherapy-induced damage to enteric neurons and gastrointestinal dysfunction have highlighted the enteric nervous system as a potential therapeutic target to alleviate chemotherapy-induced toxicity which may improve both clinical outcomes and the quality of patients' lives.

1. Introduction

The gastrointestinal (GI) tract is a vital organ imperative for digestion and absorption of nutrients and excretion of waste. Function of the GI tract is not only essential for adequate nutrition but also protection from ingested pathogens, allergens and toxins [1]. The GI tract refers to a collection of organs spanning from the mouth to the anus, which may be further sub-divided into the esophagus, stomach, small and large intestines [2]. The GI tract is a sophisticated system, comprised of several functional layers including the serosa, longitudinal muscle, myenteric plexus, circular muscle, submucosa, submucosal plexus and mucosal epithelium. These functional layers interact to enable simultaneous contraction and relaxation of the gut, facilitating adequate absorption and sensation. For these forceful and coordinated contractions to be able to occur, the smooth muscles receive input from the enteric nervous system (ENS), a component of the autonomic nervous system in the peripheral nervous system.

The ENS consists of an immense and complex network of neurons and other cells such as interstitial cells of Cajal (ICC) and enteric glial cells (EGCs) distributed along the GI tract function to regulate intestinal motility by either exciting or inhibiting GI smooth muscle [3,4]. The ENS is also responsible for other coordinated functions of the GI tract such as absorption and secretion controlled by other specialized such as secretomotor neurons and again EGC's [5]. The GI tract has sensory pathways which are critical for detecting luminal contents, to generate a response or relay sensations of fullness, pain, and discomfort. These sensory pathways include intrinsic primary afferent neurons found in the ENS, which generate an intrinsic reflex response in order to regulate motility and secretion of the GI tract as well as nerve terminals of extrinsic primary afferent neurons that are responsible in conveying signals to the central nervous system. The latest consist of vagal afferents with neuronal cell bodies in the nodose ganglion and spinal afferents with neuronal cell bodies in the dorsal root ganglia which convey sensory signals from the GI tract to the primary somatosensory cortex in the brain [6,7].

Most cancer patients receive chemotherapy either before or after surgery or in combination with radiotherapy. Although chemotherapy has greatly improved overall survival of patients with many types of cancer, GI side-effects of chemotherapy are a significant hurdle significantly affecting the clinical outcome and quality of patients' life [8,9]. GI side-effects such as nausea, vomiting, bloating, ulceration, constipation and, in particular, diarrhea are major obstacles causing

Abbreviations: CIC, chemotherapy-induced constipation; CID, chemotherapy-induced diarrhea; CRC, colorectal cancer; ENS, enteric nervous system; 5-FU, 5-fluorouracil; GI, gastrointestinal; GFAP, glial fibrillary acidic protein; ICC, interstitial cells of Cajal; IRI, irinotecan; NO, nitric oxide; OXL, oxaliplatin; ROS, reactive oxygen species

* Corresponding author.
E-mail address: Kulmira.Nurgali@vu.edu.au (K. Nurgali).

http://dx.doi.org/10.1016/j.maturitas.2017.04.021
Received 10 April 2017; Accepted 25 April 2017

Table 1
Major classes of chemotherapeutic agents.

Category name	Chemotherapeutic agents	References
Alkylating agents	Cyclophosphamide Ifosfamide Melphalan Busulfan	[30–34]
Antimetabolites	5-FU Capecitabine Methotrexate Gemcitabine	[35–38]
Anti-tumour antibiotics	Daunorubicin Doxorubicin Epirubicin	[39–41]
Topoisomerase inhibitors	Topotecan Irinotecan Etoposide Teniposide	[42–44]
Mitotic inhibitors	Paclitaxel Docetaxel Vinblastine Vincristine	[33,45–47]
Platinum-based agents	Cisplatin Carboplatin Oxaliplatin	[48–51]

delays, dose reduction and discontinuation of treatment for many cancer patients [10–12]. Although specific chemotherapeutic agents have been correlated with increased incidence of GI side-effects (Table 1), incidence of these side-effects as high as 40% in patients receiving standard dose chemotherapy and 100% in patients receiving high dose chemotherapy has been reported [13]. Furthermore, the incidence of chronic post-treatment chemotherapy-induced diarrhea (CID) and chemotherapy-induced constipation (CIC) amongst cancer survivors has been estimated to be as high as 49% with episodes persisting up to 10 years after the cessation of treatment [11,14,15].

Chemotherapy-induced GI dysfunction is particularly prevalent amongst all cancer sufferers, including colorectal cancer (CRC) patients being particularly susceptible to chemotherapy-induced diarrhea (CID) and chemotherapy-induced constipation (CIC) [16]. The most common chemotherapeutic drugs used to treat CRC patients are oxaliplatin (OXL), 5-fluorouracil (5-FU) and irinotecan (IRI), given alone or in combinations. In most cases IRI and 5-FU cause diarrhea whilst OXL induces diarrhea and constipation [8,13,17]. Both CID and CIC can be categorized into grades from 1 to 5, grading from non-life threatening to death [18]. The underlying mechanisms of CIC and CID remain unclear. Although intestinal mucositis (inflammation and ulceration of the intestinal epithelium) is a significant contributing factor, the pathophysiology of CID and CIC is likely to be complex, involving several mechanisms including changes in GI secretion, absorption and innervation. Current treatments available for both CID and CIC are dietary changes and pharmacological interventions including drugs that target the GI tract to reduce symptoms [10,13]. Many of these drugs cause severe side-effects themselves.

2. Colorectal cancer

CRC is one of the most prevalent and fatal cancers worldwide. It is the highest contributor to cancer-related death with incidence rate of approximately 1.4 million and mortality rate about 700,000 people per year globally [19,20]. Several risk factors related to environmental influences and lifestyle choices are associated with increased incidence of CRC including excessive red meat consumption, low fruit consumption, high saturated fat intake, alcohol consumption, poor hygiene and sedentary life style [21,22]. However, age is considered the primary risk factor for CRC, with incidence rates of CRC increasing steadily from 50 years of age onwards [23]. Although about 75% of colorectal tumors referred as non-familial or sporadic which do not result from inherited genetic mutations, a small proportion of colorectal tumors have been linked to mutations in oncogene *adenomatous polyposis coli (APC)* and aberrant DNA mismatch repair genes *MLH1, MSH2, PMS2* and *MSH6* [22,24].

The location and characteristics of the tumor affect clinical manifestations of CRC. In 35% of patients the primary tumours have been found proximally to the sigmoid colon making them virtually indiscernible via sigmoidoscopy [25,26]. Furthermore, clinical symptoms of CRC are non-specific and not well defined, with rectal bleeding and weight loss the only definitive symptoms [27]. Due to asymptomatic presentation of the disease, most of CRC sufferers (> 60%) are diagnosed at stage III or beyond; the prognostic outlook for these patients depends on the outcomes of chemotherapeutic treatment [28].

3. Chemotherapy

Chemotherapeutics have been used as a treatment for cancer for nearly 70 years, with the first use recorded as early as the 1940s to treat advanced lymphoma [29]. Chemotherapeutics are categorized based on their chemical structure, mechanism of action and relativeness to other drug properties (Table 1).

The effectiveness of chemotherapy is dependent upon multiple factors: the mitochondrial function of the cancer cells, tumour size, patient age, route of administration, number of chemotherapy cycles a patient goes through and the circadian cycle [29,52,53]. Anti-cancer chemotherapeutics with or without surgery are the first line of treatment for many CRC patients. Although proven to be individually effective, multi-agent regimes including leucovorin (LV), 5-FU, OXL and IRI (FOLFOX and FOLFIRI) are now the standard line of chemotherapeutic treatment for CRC and are the most promising approaches to curative and non-curative management of the disease [22,54–57]. Despite effectively improving 5 and 10 year survival rates, these chemotherapeutics are associated with undesirable side-effects significantly impacting patient quality of life [58–60].

3.1. 5-Fluorouracil

Since its discovery in the early 1960s, antimetabolite 5-FU has represented the backbone of systemic chemotherapy in the treatment of CRC [8]. The mechanism of action of 5-FU is its conversion to fluorouridine monophosphate (FUMP) by orotate phosphoribosyltransferase (OPRT) or fluorouridine (FUR). Once converted, FUMP will be phosphorylated to fluorouridine diphosphate (FUDP) and then again further phosphorylated into fluorouridine triphosphate (FUTP) as another metabolite product [37]. Once FUMP is formed, it binds at the active sites of thymidylate synthase (TS) to form a stable complex and inhibit deoxythymidine monophosphate (dTMP) production. This inhibition of dTMP causes a reduction of deoxythymidine triphosphate (dTTP), which then in turn disturbs and imbalances the levels of other deoxynucleotides that cause disruption upon the synthesis and repair of DNA, ultimately resulting in lethal damage to DNA. The other metabolite of 5-FU, FUTP has the same mechanism of action [34]. 5-FU wields its anti-proliferative effects via the inhibition of TS, resulting in cytotoxicity [61]. Approximately 40% of patients receiving 5-FU develop mucositis, a painful inflammation of the mucosal membrane, affecting the entire lining of the GI tract [37,62,63] (Table 2). Furthermore, CRC patients receiving 5-FU have a 50–80% chance of developing CID of any grade, although 30% suffer from grades 3 or 4 [8] (Table 2).

3.2. Oxaliplatin

OXL is a third-generation platinum-based drug comprised of a diaminocyclohexane carrier ligand, platinum ion, and a bidentate

Table 2
Functions and side-effects of chemotherapeutic drugs used for colorectal cancer treatment.

Chemotherapeutic agent	Function	Side-effects
5-FU	Anti-proliferating drug by inhibiting DNA synthesis [37]	Diarrhea, mucositis [13,62]
Oxaliplatin	A non-specific cell phase drug that inhibits DNA synthesis by forming cross-links of DNA molecules, which leads to strand breaks and inhibition of DNA replication [60,65]	Diarrhea, peripheral neuropathy, constipation, nausea, vomitting [18,59,60,71]
Irinotecan	Induction of permanent DNA damage to tumour cells by inhibiting DNA topoisomerase I [8]	Diarrhea, abdominal cramping, rhinitis, lacrimation, salivation, mucositis [13,62,70]

oxalate group. OXL exerts its cytotoxic effects by forming interstrand and intrastrand nuclear and mitochondrial DNA platinum adducts, particularly at the N7 position of guanine nucleotides [64–66]. Despite being more effective in the treatment of CRC than predecessor drugs cisplatin and carboplatin, OXL induces several side-effects associated with the damage to peripheral sensory and enteric nervous systems. These side-effects include sensory ataxia, functional impairment, jaw pain, eye pain, ptosis and leg cramps, nausea, vomiting, constipation and diarrhea [16,59,60,67,68] (Table 2).

3.3. Irinotecan

IRI is a DNA topoisomerase I inhibitor that elicits its cytotoxic effects via its active metabolite SN-38 prompting permanent DNA damage to tumour cells [42]. Once IRI is administered, it is firstly converted in the liver into its active metabolite 7-ethyl-10-hydroxy-camptothecin known as SN38 by two enzymes, hepatic and peripheral carboxyl esterases. Subsequently, SN-38 is glucuronidated by the enzyme hepatic uridine diphosphate glucuronosyltransferase-1A1 (UGT-1A1) to SN-38-glucuronide (SN-38G). Once SN-38G has reached the intestinal lumen it is deconjugated by bacterial ß-glucuronidase, back to its active metabolite SN38 inducing severe colonic damage including an increase in apoptosis, crypt hypoplasia, excessive mucous secretion and villus atrophy [69,70]. SN-38 and SN-38G can be excreted in urine, but fecal excretion is the major route of elimination as about 64% of total SN-38 and SN-38G metabolites are excreted via that route [13]. Despite its efficacy, IRI induces severe GI side-effects, including mucositis, abdominal cramping, lacrimation and salivation, acute diarrhea occurring within the first 24 h or delayed-onset diarrhea occurring typically 24–48 h following IRI administration [8,13,62] (Table 2).

4. Chemotherapy-induced diarrhea

CID is a common and debilitating side-effect associated with CRC chemotherapeutics [71,72]. Although the underlying pathophysiology of CID remains unclear, it is heavily associated with the development of mucositis; severe inflammation and ulceration of the mucosal epithelium [70,73]. Studies in animal models of CID have shown increased apoptosis in crypts within the jejunum and colon regions of the GI tract, and excessive secretions leading to diarrhea [74]. Moreover hypoplasia of crypt cells, reducing the number of mature secretory cells leads to increased secretion and decreased absorption capacity of the villi, further contributing to the development of diarrhea [75]. CID can be identified as uncomplicated (grades 1 and 2) with increase of stools up to 4–6 per day or complicated (grades 3 and 4) with increase of stools more than 7 per day and incontinence leading to life threatening consequences [71]. Severity of CID has been associated with several specific chemotherapeutic regimes, in particular those containing 5-FU and IRI are correlated with incidence of CID as high as 80% with one third of patients experiencing severe (grade 3 or 4) diarrhea (Table 2) [10,18].

Pharmacological interventions for CID include loperamide, octreotide and deodorized tincture of opium (DTO). Although effective, loperamide can lead to other side-effects including severe constipation, abdominal pain, dizziness, paralytic ileus and potentially worsening already present symptoms [71,76]. Octreotide is commonly used as a second line treatment due severe side-effects; uneven heart-beat, severe constipation, stomach pain and enlarged thyroid. DTO administration is associated with a plethora of side-effects including euphoria, painful urination, abdominal pain, seizures, allergic reactions, respiratory depression and constipation [71]. Despite these treatments, GI dysfunction still persists, due to the sustained damage to the ENS after the use of chemotherapeutic drugs [59,71,77].

5. Chemotherapy-induced constipation

The exact incidence of chemotherapy-induced constipation (CIC) is hard to determine due to the occurrence of secondary constipation from drugs given to inhibit other chemotherapy-induced or cancer-related symptoms such as anti-emetics to control nausea and vomiting and opioids to suppress pain. However, CIC rates as high as 80–90% have been reported following administration of cisplatin, thalidomide, and vinca alkaloids (vincristine, vinblastine and vinorelbine) [71,78]. Severe constipation can result in a variety of symptoms including abdominal distension, pain, rectal tearing, hemorrhoids, bleeding and rectal fissures when passing of dry hard stool. If left untreated, severe constipation can culminate to life threatening sequelae such as bowel obstruction, perforation, ischemia and necrosis [79,80].

Constipation can be classified into three categories: normal-transit constipation, defecatory disorders and slow-transit constipation [81]. Normal-transit constipation is the most prevalent, which presents as bloating, abdominal pain and psychosocial distress. Defecatory disorders occur when the pelvic floor or anal sphincter is dysfunctional, resulting in anal fissures and hemorrhoids. Slow-transit constipation is due to less frequent urges of needing to defecate with symptoms of abdominal pain, discomfort and bloating [71]. The pathophysiology of CIC is not intensely understood. but primarily it is due to reduction in the number of ICC and neuronal loss limiting the innervation of the internal circular and external longitudinal smooth muscles of the gut, thus, impairing normal colonic motor function, leading to constipation [82–84].

Management for constipation can be divided into two main categories with one being a non-pharmacological approach which mostly consists of lifestyle changes, such as increasing physical exercise, increasing fiber and liquid intake [85]. The pharmacological approach consists of multiple types of laxatives: bulk-forming, osmotic, emollient, stimulant, lubricant and rectal laxatives. A common side-effects of laxative use are dehydration, bloating and abdominal pain [86–88].

Thus, CID and CIC are common debilitating side-effects of chemotherapy. Current treatments for CID and CIC have many adverse effects themselves. Therefore, new approaches are required to address this problem. Since GI functions are controlled by the ENS, it is plausible to understand the role of the ENS in pathophysiology of chemotherapy-induced GI dysfunction and develop novel treatments targeting pathways involved in chemotherapy-induced ENS damage.

6. The enteric nervous system and gastrointestinal functions

The ENS is the prime regulator of the GI functions, and it extends to the other surrounding organs such as the pancreas and gall bladder. Sometimes referred to as "the second brain" due to its ability to function autonomously of the central nervous system, the ENS provides the intrinsic innervation of the GI tract. The ENS is comprised of ganglia, primary interganglionic fibre tracts as well as secondary and tertiary fibres which project to many of the effector systems of the gut including muscle cells, glands and blood vessels [5,89]. The ENS can be divided into 2 major ganglionated plexi, the myenteric (Auerbach's) and submucosal (Meissner's), which are responsible for controlling gut functions including absorption, secretion, motility and vascular tone. Furthermore, within a given plexus enteric neurons can be classified on the basis of their morphology, neurochemistry, biophysical properties, projections and connectivity [3,5].

6.1. Submucosal neurons

Situated superficially to the mucosa, the submucosal plexus is located between the circular muscle and muscularis mucosa layers and receives inputs from the myenteric plexus as well as the extrinsic sympathetic and parasympathetic nerve fibres. The neurons in the submucosal plexus innervate the mucosal epithelium and submucosal arterioles to control and maintain water and electrolyte balance, secretion and vascular tone [5,90].

Movement of fluid between the intestinal lumen and blood circulation is a complex and tightly regulated process involving neural, endocrine, paracrine, and autocrine systems [90]. Fluid is absorbed from the lumen containing nutrients via ion-coupled transporters, and returned through secretomotor reflexes. Water and electrolytes drawn from both the circulation and the absorbed fluids are moved from the interstituim of the lamina propria to the lumen. This reflexive control is exerted namely through sympathetic secretomotor and vasodilator pathways, however neural control of secretion and absorption of water and electrolytes occurs on multiple interacting levels [5].

Submucosal secretomotor neurons are directly modulated by circuitry within the myenteric plexus and via long neural reflex pathways that pass through the prevertebral sympathetic ganglia, as well as by parasympathetic and sympathetic pathways coming from the central nervous system [90]. Myenteric interneurons form a longitudinally organized recurrent excitatory network and the 5-hydroxytryptamine (5-HT)/choline acetyltransferase (ChAT) neurons in this network probably also innervate submucosal ganglia [91,92]. Similarly, myenteric intrinsic sensory neurons (ISNs) provide input to submucosal ISNs [5] and submucosal ISNs project to the myenteric plexus suggesting cross talk between the two ISN networks in any localized region of the intestine [90].

The secretory reflex involves enterochromaffin cells, ISNs, various interneurons and secretomotor neurons [93]. 5-HT released from EC cells in the mucosa acts on 5-HT3, 5-HT4, and/or 5-HT1P receptors on ISNs to activate a secretory reflex [94]. ISNs detect sensory information from the luminal environment in the form of action potentials carried in their primary afferent process. Input from ISNs converges in the submucosal plexus to activate neuropeptide Y (NPY), vasoactive intestinal peptide (VIP) and choline acetyltransferase (ChAT) immunoreactive secretomotor and/or interneurons [94]. Activation of adenylyl cyclase and resulting increase in intracellular cyclic AMP drives the opening of cystic fibrosis transmembrane conductance regulator and active chloride secretion [90].

6.2. Myenteric neurons

The myenteric plexus, located between the circular and longitudinal muscles of the muscularis externa, functions to provide motor innervation to both muscle layers of the gut [5]. Three main classes of myenteric neurons govern the complex motor reflex pathways. These include populations of ISNs (or primary afferent neurons), orally directed (ascending) and anally directed (descending) interneurons, as well as excitatory and inhibitory motor neurons supplying the circular and longitudinal muscles [5,7,95,96]. Extrinsic reflex pathways coordinate the activities of different regions of the GI tract largely by modifying the activity of enteric neurons representing a final common level of control of GI functions [95].

Motor function in the small intestine and colon is controlled by smooth muscle cells, nervous tissues and ICC [97–99]. Smooth muscle cells form an electrical syncytium within the gut and are innervated, directly or indirectly through ICC, by neurons [100]. The integration of inputs from neurons and ICC to smooth muscle cells in the GI tract allows expression of various motor patterns including peristaltic and segmenting contractions [101–103]. Peristalsis can be defined as GI motor pattern involving partial or total occlusion of the lumen that move contents in the anal direction [103]. Segmenting contractions do not result in propulsion of contents, but rather mixing activity [98].

Deficiencies in the nerve circuits as well as pathological excitation of the ENS have been shown to cause a variety of GI diseases [5,100].

7. Role of the ENS in pathology

Changes in enteric neurons are implicated in GI dysfunction associated with a plethora of disorders including achalasia, Hirschsprung's disease, intestinal neuronal dysplasia, Chagas disease, irritable bowel syndrome and severe idiopathic slow-transit constipation [5,84,100,104]. Subtle changes to the ENS, not evident in conventional histological examination, have been suggested as a potential underlying mechanism for abnormal colonic motor function leading to constipation [84]. For instance, alterations in the number of myenteric neurons expressing the excitatory neurotransmitter substance P, as well as abnormalities in the inhibitory neurotransmitters, VIP and nitric oxide (NO), and a reduction in the number of ICC have been observed in patients with slow-transit constipation [82,83,105]. Preferential changes in nitric oxide synthase (NOS) neurons have been identified in various enteric neuropathies including achalasia, diabetic gastroparesis, Chagas disease, Hirschsprung's disease and ischemia/reperfusion injury [106]. It has been suggested that the involvement of NOS neurons in enteric neuropathies is due to potentially damaging effects of the free radical, NO [106]. Due to the relationship between NO production from NOS and reactive oxygen species (ROS), generation of excessive NO is linked to oxidative stress.

Chronic intestinal inflammation has been associated with damage to the ENS resulting in a neuronal loss of up to 50% in the myenteric plexus [107,108], which may result in downstream effects on GI function. Post-inflammatory dysmotility is a well-recognized clinical entity both at the site of inflammation and at distant non-inflamed sites [109]. Both humoral and cell-mediated inflammatory responses are associated with increased excitability of enteric neurons and synaptic facilitation [110,111]. Changes to the electrophysiological properties of enteric neurons following inflammation have been demonstrated in the ileum [112,113], jejunum [114] and colon [110,115]. Motor disturbances and neuronal changes persist long after the resolution of inflammation. It has been suggested that these changes to enteric neurons contribute to disorders of motility, secretion and hypersensitivity during and following GI inflammation [100,104,108,109]. Further, several inflammatory mediators have been implicated in both short- and long-term smooth muscle contractility changes [116].

However, the effects of chemotherapeutics on enteric neurons and GI dysfunction have been largely overlooked until recently.

8. Chemotherapy-induced enteric neuropathy

Although neurotoxicity caused by different classes of chemotherapeutic drugs differs to a significant extent, neuronal degeneration and

neuropathy are emerging as key players in chemotherapy-induced GI dysfunction [17,117–121]. Significant enteric neuronal loss correlated with downstream effects on colonic motility and GI transit have been observed after administration of chemotherapeutic agents in animal models [17,119,121] Functional and structural changes in human myenteric neurons in specimens of colon from patients receiving anti-cancer chemotherapy have been reported [117]. Cisplatin administration has been found to significantly reduce the number of myenteric neurons per ganglion in the gastric fundus and distal colon [119,121]. These changes correlate with reduced upper GI transit and obliteration of colonic contractile activity caused by cisplatin treatment [119,121]. Similarly, OXL administration induces significant neuronal loss with 25% in the myenteric plexus and 21% in the submucosal plexus of the ileum and colon [118,120]. Neurons in the distal colon were more vulnerable to OXL than neurons in the ileum and proximal colon, as there was greater number of NOS-expressing neurons in the distal colon after OXL treatment, which is correlated with a reduction in muscle thickness and colonic contractile activity [17,118,120]. Alterations in the number and proportion of NOS-immunoreactive neurons have been found following both OXL and cisplatin treatment [17,119,121]. Long-term administration of OXL decreases glial fibraillary acidic protein-immunoreactive enteric glia in both myenteric and submucosal plexi, but increases s100β-immunoreactive enteric glial cells in the mouse ileum [120]. The mechanisms of neuronal damage caused by OXL involve increased superoxide production, mitochondrial membrane depolarization resulting in the release of cytochrome *c* and neuronal apoptosis [118]. OXL-induced excessive production of NO leads to enhanced inhibitory neuromuscular transmission and reduced muscle tone of the distal colon underlying colonic dysmotility and symptoms of constipation [118].

Studies investigating GI function following 5-FU administration in mice have correlated enteric neuronal loss with colonic inflammation [122]. It has been demonstrated that short-term 5-FU treatment is associated with destruction of the epithelial brush border and severe loss of colonic crypts and goblet cells; however chronic treatment did not exacerbate epithelial damage [122]. In fact, regeneration of mucosa was evident during chronic 5-FU treatment, although crypts still appeared shorter, distended and disorganized [122,123]. 5-FU-induced changes to mucosal architecture were further associated with an increased number of CD45 positive leukocytes in the colon and an amplified concentration of neutrophil gelatinase-associated protein, lipocalin-2, in faecal samples [122]. This acute inflammation following 5-FU administration was associated with loss of both excitatory (ChAT-immunoreactive) and inhibitory (NOS-immunoreactive) neurons in the myenteric plexus at later time points which coincided with delayed GI transit, gastric and intestinal emptying, and colonic dysmotility [122]. Hyperexcitability of myenteric neurons, increased number of neurons with translocation of Hu protein from the cytoplasm to the nucleus and increased soma size of NOS-immunoreactive neurons were observed in colon specimens from patients received 5-FU alone, FOLFOX (folinic acid, 5-FU and OXL) and 5-FU in combination with radiotherapy [117].

Unpublished work from our group has shown severe mucosal ulceration, crypt hypoplasia, increases in CD45 positive leukocytes and morphological disorganization in the colon after short and long-term IRI treatment (McQuade et al., 2017, unpublished). This is in line with previous studies reporting villus blunting, crypt ablation and epithelial atrophy in the rat jejunum and colon following IRI administration [124]. However, our results have demonstrated mucosal regeneration in post-treatment mice consistent with human studies showing that early histological changes in the GI tract following chemotherapeutic administration are resolved within days of treatment cessation, with no abnormal endoscopic findings in patients as early as 16 days post-chemotherapy [75]. Although histological damage to the gut may resolve within days following chemotherapeutic treatment, long-term GI dysfunction is known to persists up to 10 years following chemotherapy [11,125]. While the underlying mechanisms of this dysfunction remains unclear, early mucosal damage and acute intestinal inflammation can lead to death and damage of enteric neurons resulting in long-term GI dysfunction [107,110,112,113]. IRI administration induces significant increase in ChAT-immunoreactive neurons as well as the density of cholinergic fibers resulting in altered colonic motor activity and GI transit time (McQuade et al., 2017, unpublished).

Thus, chemotherapeutic drugs cause severe damage to the ENS significantly contributing to mechanisms underlying GI dysfunction.

9. Conclusion and future prospects

Chemotherapy-induced GI dysfunction is a serious yet underacknowledged clinical hurdle impacting the effective treatment of CRC. Persistent and chronic constipation and diarrhea in particular significantly influence effective application of chemotherapeutics, contributing to dose reductions, dose delays and cessation of chemotherapeutic treatment in a large majority of CRC patients. Understanding pathophysiological mechanisms underlying these dose-limiting symptoms and the development of new therapies targeting these mechanisms is a promising avenue of research that may improve the prognostic outcome of CRC. Recent studies providing insight into the association between chemotherapy-induced enteric neuropathy and GI dysfunction have highlighted the ENS as a potential therapeutic target for alleviating chemotherapy-induced toxicity which may improve both clinical outcomes and quality of life in CRC patients.

Contributors

JE and RMMcQ wrote the article and contributed equally to the paper.

VS and KN edited and reviewed the article.

KN conceived the idea for this review.

Conflicts of interest

The authors have no conflict of interest to declare.

Funding

No funding was received specifically for this review.

Provenance and peer review

This article has undergone peer review.

Acknowledgements

The authors would like to thank the Centre for Chronic Disease and the College of Health and Biomedicine for support and discussions.

References

[1] A. Goldstein, R. Hofstra, A. Burns, Building a brain in the gut: development of the enteric nervous system, Clin. Genet. 83 (4) (2013) 307–316.
[2] K. Moore, A. Agur, A. Dalley, Essential Clinical Anatomy, 6th ed., Lippincott Williams & Wilkins, Philadelphia, 2013.
[3] M. Costa, S. Brookes, Architecture of enteric neural circuits involved in intestinal motility, Eur. Rev. Med. Pharmacol. Sci. 12 (2008) 3–19.
[4] K. Sanders, S. Koh, S. Ro, S. Ward, Regulation of gastrointestinal motility—insights from smooth muscle biology, Nat. Rev. Gastroenterol. Hepatol. 9 (11) (2012) 633–645.
[5] J.B. Furness, The enteric nervous system and neurogastroenterology, Nat. Rev. Gastroenterol. Hepatol. 9 (2012) 286–294.
[6] S. Brookes, N. Spencer, M. Costa, V. Zagorodnyuk, Extrinsic primary afferent signalling in the gut, Nat. Rev. Gastroenterol. Hepatol. 10 (5) (2013) 286–296.
[7] J. Furness, C. Jones, K. Nurgali, N. Clerc, Intrinsic primary afferent neurons and nerve circuits within the intestine, Prog. Neurobiol. 72 (2) (2004) 143–164.
[8] C.S. Lee, E.J. Ryan, G.A. Doherty, Gastro-intestinal toxicity of chemotherapeutics in colorectal cancer: the role of inflammation, World J. Gastroenterol. 20 (14) (2014) 3751–3761.

[9] H. Xue, M.B. Sawyer, P.E. Wischmeyer, V.E. Baracos, Nutrition modulation of gastrointestinal toxicity related to cancer chemotherapy from preclinical findings to clinical strategy, JPEN J. Parenter. Enteral Nutr. 35 (2011) 74–90.
[10] A.B. Benson, J.A. Ajani, R.B. Catalano, C. Engelking, S.M. Kornblau, J.A. Martenson, et al., Recommended guidelines for the treatment of cancer treatment-induced diarrhea, J. Clin. Oncol. 22 (2004) 2918–2926.
[11] C.S. Denlinger, A.M. Barsevick, The challenges of colorectal cancer survivorship, J. Natl. Compr. Cancer Netw. 7 (2009) 883–894.
[12] D. Peterson, C.B. Boers-Doets, R.J. Bensadoun, J. Herrstedt, Management of oral and gastrointestinal mucosal injury: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up, Ann. Oncol. (Suppl. 5) (2015) v139–v151.
[13] A. Stein, W. Voigt, K. Jordan, Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management, Ther. Adv. Med. Oncol. 2 (1) (2010) 51–63.
[14] A.R. Kim, J. Cho, Y.-J. Hsu, M.G. Choi, J.H. Noh, T.S. Sohn, et al., Changes of quality of life in gastric cancer patients after curative resection: a longitudinal cohort study in Korea, Ann. Surg. 256 (2012) 1008–1013.
[15] E.C. Schneider, J.L. Malin, K.L. Kahn, C.Y. Ko, J. Adams, A.M. Epstein, Surviving colorectal cancer, Cancer 110 (2007) 2075–2082.
[16] R.M. McQuade, J.C. Bornstein, K. Nurgali, Anti-colorectal cancer chemotherapy-induced diarrhoea: current treatments and side-effects, Int. J. Clin. Med. 5 (2014) 393–406.
[17] L. Wafai, M. Taher, V. Jovanovska, J.C. Bornstein, C. Dass, K. Nurgali, Effects of oxaliplatin on mouse myenteric neurons and colonic motility, Front. Neurosci. 7 (2013) 30.
[18] G. Richardson, R. Dobish, Chemotherapy induced diarrhea, J. Oncol. Pharm. Pract. 13 (4) (2007) 181–198.
[19] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, et al., Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, Int. J. Cancer 136 (2015) E359–E386.
[20] World Cancer Report 2014, International Agency for Research on Cancer (IARC), 2014.
[21] E. Giovannucci, Modifiable risk factors for colon cancer, Gastroenterol. Clin. North Am. 31 (4) (2002) 925–943.
[22] G. Binefa, Colorectal cancer: from prevention to personalized medicine, World J. Gastroenterol. 20 (22) (2014) 6786.
[23] P.L. McClements, V. Madurasinghe, C.S. Thomson, C.G. Fraser, F.A. Carey, R.J. Steele, G. Lawrence, D.H. Brewster, Impact of the UK colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends, Cancer Epidemiol. 6 (4) (2012) e232–42.
[24] V. Gorbunova, A. Seluanov, Z. Mao, C. Hine, Changes in DNA repair during aging, Nucleic Acids Res. 35 (22) (2007) 7466–7474.
[25] J.M. Church, Colon cancer screening update and management of the malignant polyp, Clin. Colon Rectal Surg. 18 (2005) 141.
[26] K. McCallion, R. Mitchell, R. Wilson, F. Kee, R. Watson, J. Collins, K. Gardiner, Flexible sigmoidoscopy and the changing distribution of colorectal cancer: implications for screening, Gut 48 (2001) 522–525.
[27] B.-A. Adelstein, P. Macaskill, S. Chan, P. Katelaris, L. Irwig, Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review, BMC Gastroenterol. 11 (2011) 65.
[28] R. Siegel, C. Desantis, A. Jemal, Colorectal cancer statistics, CA. Cancer J. Clin. 64 (2014) 104–117.
[29] K. Sak, Chemotherapy and dietary phytochemical agents, Chemother. Res. Pract. 2012 (2012) 282570.
[30] M. Furlanut, L. Franceschi, Pharmacology of ifosfamide, Oncology 65 (2) (2003) 2–6.
[31] T. Iwamoto, Y. Hiraku, S. Oikawa, H. Mizutani, M. Kojima, S. Kawanishi, DNA intrastrand cross-link at the 5′-GA-3′ sequence formed by busulfan and its role in the cytotoxic effect, Cancer Sci. 95 (5) (2004).
[32] V.J. Spanswick, C. Craddock, M. Sekhar, P. Mahendra, P. Shankaranarayana, R.G. Hughes, D. Hochhauser, J.A. Hartley, Repair of DNA interstrand crosslinks as a mechanism of clinical resistance to melphalan in multiple myeloma, Blood 100 (2002) 224–229.
[33] X. Wu, A new classification system of anticancer drugs – based on cell biological mechanisms, Med. Hypotheses 66 (5) (2006) 883–887.
[34] N. Zhang, Y. Yin, S. Xu, W. Chen, 5-Fluorouracil: mechanisms of resistance and reversal strategies, Molecules 13 (8) (2008) 1551–1569.
[35] A. Bergman, A. Adema, J. Balzarini, S. Bruheim, I. Fichtner, P. Noordhuis, et al., Antiproliferative activity and mechanism of action of fatty acid derivatives of gemcitabine in leukemia and solid tumor cell lines and in human xenografts, Invest. New Drugs 29 (3) (2011) 456–466.
[36] D.B. Longley, D.P. Harkin, P.G. Harkin, 5-fluorouracil: mechanisms of action and clinical strategies, Nat. Rev. Cancer 3 (2003) 330–338.
[37] M. Panczyk, Pharmacogenetics research on chemotherapy resistance in colorectal cancer over the last 20 years, World J. Gastroenterol. 20 (29) (2014) 9775–9827.
[38] G. Yao, L. Cao, M. Liu, L. Chen, X. Hu, C. Ye, Gemcitabine and capecitabine combination chemotherapy in patients with metastatic breast cancer pretreated with anthracyclines and/or taxanes, Chemotherapy 61 (4) (2016) 171–178.
[39] E. Caliò, P. Seminara, T. Aronne, E. Sbaffi, V. Pagani Guazzugli Bonaiuti, L. Gargano, F. Franchi, In vitro models of a three-drug regimen (epirubicin, cisplatin and fluorouracil) for the treatment of colorectal cancer, Chemotherapy 47 (6) (2001) 430–437.
[40] T. Jackson, Intracellular accumulation and mechanism of action of doxorubicin in a spatio-temporal tumor model, J. Theor. Biol. 220 (2) (2003) 201–213.
[41] F. Wang, X. Liu, C. Liu, Z. Liu, L. Sun, Effects of antibiotic antitumor drugs on nucleotide levels in cultured tumor cells: an exploratory method to distinguish the mechanisms of antitumor drug action based on targeted metabolomics, Acta Pharm. Sin. B 5 (3) (2015) 223–230.
[42] S. Chen, N. Chan, T. Hsieh, New mechanistic and functional insights into DNA topoisomerases, Annu. Rev. Biochem 82 (1) (2013) 139–170.
[43] F. Crea, E. Giovannetti, F. Cortesi, V. Mey, S. Nannizzi, M. Gallegos Ruiz, et al., Epigenetic mechanisms of irinotecan sensitivity in colorectal cancer cell lines, Mol. Cancer Ther. 8 (7) (2009) 1964–1973.
[44] K. Kadoyama, A. Kuwahara, M. Yamamori, J. Brown, T. Sakaeda, Y. Okuno, Hypersensitivity reactions to anticancer agents: data mining of the public version of the FDA adverse event reporting system, AERS J. Exp. Clin. Cancer Res. 30 (1) (2011) 93.
[45] J. Choi, B. Jo, Enhanced paclitaxel bioavailability after oral administration of pegylated paclitaxel prodrug for oral delivery in rats, Int. J. Pharm. 280 (1–2) (2004) 221–227.
[46] M. Jordan, Mechanism of action of antitumor drugs that interact with microtubules and tubulin, Curr. Med. Chem.-Anti-Cancer Agents 2 (1) (2002) 1–17.
[47] A. Raciborska, K. Bilska, K. Drabko, R. Chaber, M. Pogorzala, E. Wyrobek, et al., Vincristine, irinotecan, and temozolomide in patients with relapsed and refractory Ewing sarcoma, Pediatr. Blood Cancer 60 (10) (2013) 1621–1625.
[48] S.P. Basourakos, L. Li, A.M. Aparicio, P.G. Corn, J. Kim, T.C. Thompson, Combination platinum-based and DNA damage response-targeting cancer therapy: evolution and future directions, Curr. Med. Chem. (2016) [Epub ahead of print].
[49] S. Dasari, P.B. Tchounwou, Cisplatin in cancer therapy: molecular mechanisms of action, Eur. J. Pharmacol. 740 (2014) 364–378.
[50] M. Graham, G. Lockwood, D. Greenslade, S. Brienza, M. Bayssas, E. Gamelin, Clinical pharmacokinetics of oxaliplatin: a critical review, Clin. Cancer Res. 6 (2000) 1205–1218.
[51] Y. Xiong, B.Y. Huang, J.Y. Yin, Pharmacogenomics of platinum-based chemotherapy in non-small cell lung cancer: focusing on DNA repair systems, Med. Oncol. 34 (4) (2017) 48.
[52] A. Ahmad, S. Banerjee, Z. Wang, D. Kong, A. Majumdar, F. Sarkar, Aging and inflammation: etiological culprits of cancer, Curr. Aging Sci. 2 (3) (2009) 174–186.
[53] F. Lévi, E. Filipski, I. Iurisci, X. Li, P. Innominato, Cross-talks between circadian timing system and cell division cycle determine cancer biology and therapeutics, Cold Spring Harb. Symp. Quant. Biol. 72 (1) (2007) 465–475.
[54] A. De Gramont, A. Figer, M. Seymour, M. Homerin, A. Hmissi, J. Cassidy, et al., Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer, J. Clin. Oncol. 18 (16) (2000) 2938–2947.
[55] R. Goldberg, Advances in the treatment of metastatic colorectal cancer, Oncol. 10 (Suppl.3) (2005) 40–48.
[56] A. Grothey, D. Sargent, R. Goldberg, H. Schmoll, Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment, J. Clin. Oncol. 22 (7) (2004) 1209–1214.
[57] C. Tournigand, T. André, E. Achille, G. Lledo, M. Flesh, D. Mery-Mignard, et al., FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study, J. Clin. Oncol. 22 (2) (2004) 229–237.
[58] R. McQuade, V. Stojanovska, J.C. Bornstein, K. Nurgali, Colorectal cancer chemotherapy: the evolution of treatment and new approaches, Curr. Med. Chem. (2017) [Epub ahead of print].
[59] V. Stojanovska, S. Sakkal, K. Nurgali, Platinum-based chemotherapy: gastrointestinal immunomodulation and enteric nervous system toxicity, Am. J. Physiol.: Gastrointest. Liver Physiol. 308 (4) (2014) G223–G232.
[60] A. Weickhardt, K. Wells, W. Messersmith, Oxaliplatin-induced neuropathy in colorectal cancer, J. Oncol. 2011 (2011) 201593.
[61] D. Das, R. Preet, P. Mohapatra, S. Satapathy, S. Siddharth, T. Tamir, et al., 5-Fluorouracil mediated anti-cancer activity in colon cancer cells is through the induction of Adenomatous Polyposis Coli: implication of the long-patch base excision repair pathway, DNA Repair 24 (2014) 15–25.
[62] Y. Kwon, Mechanism-based management for mucositis: option for treating side effects without compromising the efficacy of cancer therapy, OncoTargets Ther. 9 (2016) 2007–2016.
[63] S. Sonis, The pathobiology of mucositis, Nat. Rev. Cancer 4 (4) (2004) 277–284.
[64] S. McWhinney, R. Goldberg, H. McLeod, Platinum neurotoxicity pharmacogenetics, Mol. Cancer Ther. 8 (1) (2009) 10–16.
[65] N. Miltenburg, W. Boogerd, Chemotherapy-induced neuropathy: a comprehensive survey, Cancer Treat. Rev. 40 (7) (2014) 872–882.
[66] J. Park, J. Chae, K. Roh, E. Kil, M. Lee, C. Auh, et al., Oxaliplatin-induced peripheral neuropathy via TRPA1 stimulation in mice dorsal root ganglion is correlated with aluminum accumulation, PLoS One 10 (4) (2015) e0124875.
[67] V. Carozzi, A. Canta, A. Chiorazzi, Chemotherapy-induced peripheral neuropathy: what do we know about mechanisms, Neurosci. Lett. 596 (2015) 90–107.
[68] R. Cersosimo, Oxaliplatin-associated neuropathy: a review, Ann. Pharmacother. 39 (1) (2005) 128–135.
[69] A.M. Stringer, R. Gibson, J.M. Bowen, D. Keefe, Chemotherapy-induced modifications to gastrointestinal microflora: evidence and implications of change, Curr. Drug Metab. 10 (2009) 79–83.
[70] A. Stringer, R. Gibson, R. Logan, J. Bowen, A. Yeoh, J. Laurence, D. Keefe, Irinotecan-induced mucositis is associated with changes in intestinal mucins, Cancer Chemother. Pharmacol. 64 (1) (2009) 123–132.
[71] R. McQuade, V. Stojanovska, R. Abalo, J.C. Bornstein, K. Nurgali, Chemotherapy-induced constipation and diarrhea: pathophysiology, current and emerging treatments, Front. Pharmacol. 7 (2016) 414.
[72] R. Gibson, D. Keefe, Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies, Support. Care Cancer 14 (9)

(2006) 890–900.
[73] R. Gibson, J. Coller, H. Wardill, M. Hutchinson, S. Smid, J. Bowen, Chemotherapy-induced gut toxicity and pain: involvement of TLRs, Support. Care Cancer 24 (5) (2015) 2251–2258.
[74] R. Gibson, J. Bowen, M. Inglis, A. Cummins, D. Keefe, Irinotecan causes severe small intestinal damage, as well as colonic damage, in the rat with implanted breast cancer, J. Gastroenterol. Hepatol. 18 (9) (2003) 1095–1100.
[75] D. Keefe, J. Brealey, G. Goland, A. Cummins, Chemotherapy for cancer causes apoptosis that precedes hypoplasia in crypts of the small intestine in humans, Gut 47 (2000) 632–637.
[76] R. Sharma, P. Tobin, S. Clarke, Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea, Lancet Oncol. 6 (2) (2005) 93–102.
[77] D. Thorpe, A. Stringer, R. Butler, Chemotherapy-induced mucositis: the role of mucin secretion and regulation, and the enteric nervous system, Neuro Toxicol. 38 (2013) 101–105.
[78] I.M. Ghobrial, S.V. Rajkumar, Management of thalidomide toxicity, J. Support. Oncol. 1 (2003) 194.
[79] L. Leung, T. Riutta, J. Kotecha, W. Rosser, Chronic constipation: an evidence-based review, J. Am. Board Fam. Med. 24 (2011) 436–451.
[80] A. MacDonald, M. Shearer, P. Paterson, I. Finlay, Relationship between outlet obstruction constipation and obstructed urinary flow, Br. J. Surg. 78 (1991) 693–695.
[81] A. Lembo, M. Camilleri, Chronic constipation, N. Engl. J. Med. 349 (2003) 1360–1368.
[82] C.L. He, L. Burgart, L. Wang, J. Pemberton, T. Young-Fadok, J. Szurszewski, G. Farrugia, Decreased interstitial cell of Cajal volume in patients with slow-transit constipation, Gastroenterology 118 (2000) 14–21.
[83] K. Tzavella, R.L. Riepl, A.G. Klauser, W.A. Voderholzer, N.E. Schindlbeck, S.A. Müller-Lissner, Decreased substance P levels in rectal biopsies from patients with slow transit constipation, Eur. J. Gastroenterol. Hepatol. 8 (1996) 1207–1211.
[84] G. Bassotti, V. Villanacci, Can functional constipation be considered as a form of enteric neuro-gliopathy, Glia 59 (2011) 345–350.
[85] I. Mancini, E. Bruera, Constipation in advanced cancer patients, Support. Care Cancer 6 (1998) 356–364.
[86] J.G. Avila, Pharmacologic treatment of constipation in cancer patients, Cancer Control 11 (2004) 10–18.
[87] V.C. Costilla, A.E. Foxx-Orenstein, Constipation: understanding mechanisms and management, Clin. Geriatr. Med. 30 (2014) 107–115.
[88] R. Twycross, N. Sykes, M. Mihalyo, A. Wilcock, Stimulant laxatives and opioid-induced constipation, J. Pain Symptom Manag. 43 (2012) 306–313.
[89] M.B. Hansen, The enteric nervous system II: gastrointestinal functions, Pharmacol. Toxicol. 92 (2003) 249–257.
[90] J. Bornstein, R. Gwynne, H. Sjovall, Enteric neural regulation of mucosal secretion, 5th edition, Physiology of the Gastrointestinal Tract vol. 1, (2012).
[91] K. Neal, J. Bornstein, Mapping 5-HT inputs to enteric neurons of the guinea-pig small intestine, Neuroscience 145 (2007) 556–567.
[92] K. Neal, J. Bornstein, Targets of myenteric interneurons in the guinea-pig small intestine, Neurogastroenterol. Motil. 20 (2008) 566–575.
[93] F.L. Christofi, Purinergic receptors and gastrointestinal secretomotor function, Purinergic Signal. 4 (2008) 213–236.
[94] S. Vanner, W. Macnaughton, Submucosal secretomotor and vasodilator reflexes, Neurogastroenterol. Motil. 16 (2004) 39–43.
[95] J. Bornstein, J. Furness, W. Kunze, P. Bertrand, Enteric reflexes that influence motility, Innervation Gastrointest. Tract (2002) 1–55.
[96] J.C. Bornstein, Intrinsic sensory neurons of mouse gut—toward a detailed knowledge of enteric neural circuitry across species. Focus on characterization of myenteric sensory neurons in the mouse small intestine, J. Neurophysiol. 96 (2006) 973–974.
[97] W.L. Hasler, Motility of the small intestine and colon, Textb. Gastroenterol. 1 (1999) 215–245.
[98] J.D. Huizinga, J.H. Chen, The myogenic and neurogenic components of the rhythmic segmentation motor patterns of the intestine, Front. Neurosci. 8 (2014) 1–8.
[99] M. Takaki, Gut pacemaker cells: the interstitial cells of Cajal (ICC), J. Smooth Muscle Res. 39 (5) (2003) 137–161.
[100] R. De Giorgio, The human enteric nervous system in health and disease, Auton. Neurosci.: Basic Clin. 192 (2015) 3–4.
[101] P. Dinning, T. Smith, S. Scott, Pathophysiology of colonic causes of chronic constipation, Neurogastroenterol. Motil. 21 (2009) 20–30.
[102] R.M. Gwynne, E. Thomas, S. Goh, H. Sjövall, J. Bornstein, Segmentation induced by intraluminal fatty acid in isolated guinea-pig duodenum and jejunum, J. Physiol. 556 (2004) 557–569.
[103] J.D. Huizinga, W.J. Lammers, Gut peristalsis is governed by a multitude of cooperating mechanisms, Am. J. Physiol.: Gastrointest. Liver Physiol. 296 (2009) 1–8.
[104] C. Knowles, G. Lindberg, E. Panza, R. De Giorgio, New perspectives in the diagnosis and management of enteric neuropathies, Nat. Rev. Gastroenterol. Hepatol. 10 (4) (2013) 206–218.
[105] C. Cortesini, F. Cianchi, A. Infantino, M. Lise, Nitric oxide synthase and VIP distribution in enteric nervous system in idiopathic chronic constipation, Dig. Dis. Sci. 40 (1995) 2450–2455.
[106] L. Rivera, D. Poole, M. Thacker, J. Furness, The involvement of nitric oxide synthase neurons in enteric neuropathies, Neurogastroenterol. Motil. 23 (2011) 980–988.
[107] L. Boyer, M. Ghoreishi, V. Templeman, B.A. Vallance, A.M. Buchan, G. Jevon, K. Jacobson, Myenteric plexus injury and apoptosis in experimental colitis, Auton. Neurosci. 117 (1) (2005) 41–53.
[108] G.M. Mawe, K.A. Sharkey, The intrinsic reflex circuitry of the inflamed colon, Adv. Exp. Med. Biol. 891 (2016) 153–157.
[109] G.M. Mawe, Colitis-induced neuroplasticity disrupts motility in the inflamed and post-inflamed colon, J. Clin. Invest. 125 (3) (2015) 949–955.
[110] D. Linden, K. Sharkey, G. Mawe, Enhanced excitability of myenteric AH neurones in the inflamed guinea-pig distal colon, J. Physiol. 547 (2) (2003) 589–601.
[111] K. Nurgali, T.V. Nguyen, M. Thacker, L. Pontell, J.B. Furness, Slow synaptic transmission in myenteric AH neurons from the inflamed guinea pig ileum, Am. J. Physiol.: Gastrointest. Liver Physiol. 297 (2009) G582–G593.
[112] K. Nurgali, T.V. Nguyen, H. Matsuyama, M. Thacker, H.L. Robbins, J.B. Furness, Phenotypic changes of morphologically identified myenteric neurons following intestinal inflammation, J. Physiol. 583 (2) (2007) 593–609.
[113] K. Nurgali, Z. Qu, B. Hunne, M. Thacker, L. Pontell, J.B. Furness, Morphological and functional changes in the guinea-pig neurons projecting to the ileal mucosa at early stages after inflammatory damage, J. Physiol. 589 (2) (2011) 325–339.
[114] J.M. Palmer, M. Wong-Riley, K.A. Sharkey, Functional alterations in jejunal myenteric neurons during inflammation in nematode-infected guinea pigs, Am. J. Physiol. 275 (5 Pt 1) (1998) G922–35.
[115] A.E. Lomax, J.R. O'Hara, N.P. Hyland, G.M. Mawe, K.A. Sharkey, Persistent alterations to enteric neural signaling in the guinea pigcolon following the resolution of colitis, Am. J. Physiol.: Gastrointest. Liver Physiol. 292 (2) (2007) G482–G491.
[116] I. Demedts, K. Geboes, S. Kindt, P. Vanden Berghe, A. Andrioli, J. Janssens, J. Tack, Neural mechanisms of early postinflammatory dysmotility in rat small intestine, Neurogastroenterol. Motil. 18 (12) (2006) 1102–1111.
[117] S.E. Carbone, V. Jovanovska, S.J.H. Brookes, K. Nurgali, Electrophysiological and morphological changes in colonic myenteric neurons from chemotherapy-treated patients: a pilot study, Neurogastroenterol. Motil. 28 (7) (2016) 975–984.
[118] R. McQuade, S. Carbone, V. Stojanovska, A. Rahman, R. Gwynne, A. Robinson, et al., Role of oxidative stress in oxaliplatin-induced enteric neuropathy and colonic dysmotility in mice, Br. J. Pharmacol. 173 (24) (2016) 3502–3521.
[119] A. Pini, R. Garella, E. Idrizaj, L. Calosi, M. Baccari, M. Vannucchi, Glucagon-like peptide 2 counteracts the mucosal damage and the neuropathy induced by chronic treatment with cisplatin in the mouse gastric fundus, Neurogastroenterol. Motil. 28 (2) (2015) 206–216.
[120] A. Robinson, V. Stojanovska, A. Rahman, R. McQuade, P. Senior, K. Nurgali, Effects of Oxaliplatin treatment on the enteric glial cells and neurons in the mouse ileum, J. Histochem. Cytochem. 64 (9) (2016) 530–545.
[121] G. Vera, M. Castillo, P. Cabezos, A. Chiarlone, M. Martín, A. Gori, et al., Enteric neuropathy evoked by repeated cisplatin in the rat, Neurogastroenterol. Motil. 23 (4) (2011) 370-e163.
[122] R. McQuade, V. Stojanovska, E. Donald, R. Abalo, J.C. Bornstein, K. Nurgali, Gastrointestinal dysfunction and enteric neurotoxicity following treatment with anticancer chemotherapeutic agent 5-fluorouracil, Neurogastroenterol. Motil. 28 (12) (2016) 1861–1875.
[123] P. Soares, J. Mota, A. Gomes, R. Oliveira, A. Assreuy, G. Brito, et al., Gastrointestinal dysmotility in 5-fluorouracil-induced intestinal mucositis outlasts inflammatory process resolution, Cancer Chemother. Pharmacol. 63 (1) (2008) 91–98.
[124] R.M. Logan, R.J. Gibson, J.M. Bowen, A.M. Stringer, S.T. Sonis, D.M. Keefe, Characterisation of mucosal changes in the alimentary tract following administration of irinotecan: implications for the pathobiology of mucositis, Cancer Chemother. Pharmacol. 62 (2008) 33–41.
[125] G. Numico, V. Longo, G. Courthod, N. Silvestris, Cancer survivorship: long-term side-effects of anticancer treatments of gastrointestinal cancer, Curr. Opin. Oncol. 27 (4) (2015) 351–357.