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REVIEW

The gut–brain axis in vertebrates: implications for food intake regulation

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ABSTRACT

The gut and brain are constantly communicating and influencing each other through neural, endocrine and immune signals in an interaction referred to as the gut–brain axis. Within this communication system, the gastrointestinal tract, including the gut microbiota, sends information on energy status to the brain, which, after integrating these and other inputs, transmits feedback to the gastrointestinal tract. This allows the regulation of food intake and other physiological processes occurring in the gastrointestinal tract, including motility, secretion, digestion and absorption. Although extensive literature is available on the mechanisms governing the communication between the gut and the brain in mammals, studies on this axis in other vertebrates are scarce and often limited to a single species, which may not be representative for obtaining conclusions for an entire group. This Review aims to compile the available information on the gut–brain axis in birds, reptiles, amphibians and fish, with a special focus on its involvement in food intake regulation and, to a lesser extent, in digestive processes. Additionally, we will identify gaps of knowledge that need to be filled in order to better understand the functioning and physiological significance of such an axis in non-mammalian vertebrates.

KEY WORDS: Gastrointestinal tract, Enteroendocrine cells, Microbiota, Non-mammals

Introduction

The term ‘gut–brain axis’ refers to a complex bidirectional communication system between the gastrointestinal tract and the central nervous system (CNS). This system ensures the proper maintenance of gastrointestinal homeostasis and probably affects higher cognitive functions, such as affect and motivation (Rhee et al., 2009). Within this axis, at least in mammals, the gastrointestinal tract sends information (mainly on energy status) to the brain, which integrates this with input from other systems and transmits feedback to the gastrointestinal tract. This feedback serves to regulate food intake and other physiological processes taking place in the gastrointestinal tract (e.g. motility, secretion, digestion, absorption), which helps to maintain energy homeostasis (Carabotti et al., 2015; Cryan et al., 2019; Rhee et al., 2009). The bidirectional crosstalk between the gut and brain involves, on the one hand, neural signals (neurotransmitters), which are transmitted mainly via the vagus nerve of the autonomic nervous system. On the other hand, endocrine (hormone) and immune (cytokine) signals can either activate receptors on peripheral endings of sensory nerves or be transported by the blood to the brain or gut (as applicable) and directly act on the target tissue (Mayer, 2011; Parker et al., 2020). Moreover, recent studies demonstrated that the gut microbiota plays an important role in the gut–brain axis, interacting not only locally with intestinal cells (mainly immune cells, enteroendocrine cells and enterocytes) and the enteric nervous system (ENS), but also directly with the brain through neuroendocrine and metabolic pathways (Petschow et al., 2013; Wang and Wang, 2016). In turn, the brain modulates the community structure and function of gut microbiota, either indirectly through an autonomic nervous system-mediated modulation of intestinal processes, or directly through the luminal secretion of hormones, which can modulate microbial gene expression (Martin et al., 2018). The gut–brain axis has been extensively studied in mammalian models, but knowledge about this axis in non-mammalian vertebrates is scarce (Fig. 1). This Review aims to offer a brief overview of the gut–brain axis in mammals and to describe, from a comparative point of view, what is known at present about the existence of such an axis in birds, reptiles, amphibians and fish. We focus on its involvement in the control of food intake and, to a lesser extent, in digestive processes occurring in the gastrointestinal tract. We will divide the Review into three sections. First, we will discuss the communication mechanisms taking place from the gut to the brain. Among the three basic signalling mechanisms (neuronal, endocrine and immune-related) occurring within the gut–brain axis, this section will concentrate on endocrine (and paracrine) signalling, which has known roles in appetite regulation. Second, we will describe the brain-to-gut communication pathways. This connection does not directly influence food intake, but it is more related to the modulation of gastrointestinal processes occurring post-prandially (see Glossary), among which we will concentrate on gut motility and secretion. Finally, we will discuss the available literature on the role of gut microbiota in controlling food intake. It is worth mentioning that much of the available knowledge in non-mammals derives from a single study or a group of studies carried out in a single species; thus, results may not be representative for the entire group. This highlights the need for further research on the gut–brain axis in non-mammalian vertebrates.

Endocrine connection from the gut to the brain

The mucosa of the gastrointestinal tract contains specialised cells with endocrine functions, often referred to as enteroendocrine cells (EECs). At least in mammals, these cells are capable of sensing luminal content and producing and releasing signalling molecules, which can exert local or distal responses, as detailed below (Fig. 2). Although EECs comprise only ∼1% of all gut epithelial cells, the enteric endocrine system can be considered to represent the largest endocrine organ in the body (Ahlman and Nilsson, 2001). Depending on their morphology, EECs are classified into ‘open’ and ‘closed’ types. The open-type EECs are bottle-shaped cells that occupy the entire width of the mucosa, and have an apical extension with microvilli that stretch into the intestinal lumen, making direct contact with the intestinal contents. In contrast, the closed-type

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Glossary

Agouti-related protein (AgRP)
Neuropeptide synthesised and released by neuropeptide Y and AgRP neurons in the arcuate nucleus of the hypothalamus. It acts, together with neuropeptide Y, to increase appetite and decrease metabolism and energy expenditure.

Anorexigenic
Drug, hormone or compound that decreases appetite.

Cholecystokinin (CCK)
Peptide hormone synthesised and secreted by enteroendocrine cells that are located mainly in the anterior part of the intestine, responsible for stimulating the digestion of fat and protein.

Cocaine- and amphetamine-regulated transcript (CART)
Neuropeptide synthesised and released by proopiomelanocortin and CART neurons in the arcuate nucleus of the hypothalamus. It acts, together with proopiomelanocortin-derived neuropeptides, to decrease appetite and increase metabolism and energy expenditure.

Ghrelin
Peptide hormone synthesised and secreted mainly in the stomach (or its equivalent in stomachless species), which has been implicated in a wide variety of physiological functions. Regarding food intake, ghrelin is the most potent stimulator of food intake from the periphery, although an inhibitory role of food intake by ghrelin has been reported for some species (e.g. most birds, some fish).

Glucagon-like peptide-1 (GLP-1)
Peptide hormone synthesised and secreted by enteroendocrine cells that are located mainly in the distal small intestine (jejunum and ileum) and large intestine in response to the ingestion of carbohydrates and lipids, and less pronouncedly in response to proteins. GLP-1 contributes to post-prandial glucose clearance in mammals and plays a role in suppressing food intake in all vertebrate groups studied so far (mammals, birds and fish).

Glucosensor
Transporter, receptor or other compound able to detect glucose levels in the body.

Median eminence
Small swelling at the base of the hypothalamus where hypothalamic hormones converge onto the portal capillary system that vascularises the anterior pituitary gland to modulate pituitary hormonal secretion.

Neuropeptide Y (NPY)
Neuropeptide synthesised and released by NPY and AgRP neurons in the arcuate nucleus of the hypothalamus. It acts, together with AgRP, to increase appetite and decrease metabolism and energy expenditure.

Orexigenic
Drug, hormone or compound that increases appetite.

Orexin (also known as hypocretin)
Neuropeptide synthesised by the hypothalamus; increases food intake and regulates arousal and wakefulness.

Parasympathetic nervous system
Part of the autonomic nervous system containing mainly cholinergic fibres; tends to induce secretion, increase the tone and contractility of smooth muscle and slow heart rate.

Peptide tyrosine tyrosine (PYY)
Peptide hormone synthesised and secreted by enteroendocrine cells located mainly in the distal small intestine (jejunum and ileum) and large intestine in response to feeding. Its main physiological function is to reduce food intake.

Post-prandially
Occurring after a meal.

Proopiomelanocortin (POMC)
Precursor polypeptide synthesised by POMC/CART neurons in the arcuate nucleus of the hypothalamus, from which melanocortins (alpha-, beta- and gamma-melanocyte stimulating hormones, MSHs) and the adrenocorticotropic hormone (ACTH) are derived. Melanocortins act, together with CART, to decrease appetite and increase metabolism and energy expenditure.

Pyloric caeca
Organ with finger-like projections located near the junction of the stomach and the intestine in some fishes. Its function is not entirely understood, but it is known to secrete enzymes that aid in digestion.

Sympathetic nervous system
Part of the autonomic nervous system containing mainly adrenergic fibres; tends to depress secretion, decrease the tone and contractility of smooth muscle, and increase heart rate.

EECs are located close to the basal membrane, lack microvilli and do not reach into the gut lumen; instead, they are believed to secrete signalling molecules in response to indirect activation by luminal content through neural or humoral pathways (Gribble and Reimann, 2016; Latorre et al., 2016). Both open- and closed-type EECs store their secretory products in cytoplasmatic granules and release them by exocytosis at the basolateral membrane in response to mechanical, chemical or neural stimulation (Latorre et al., 2016). In addition to this morphological classification, EECs are traditionally classified based on the major signalling molecule they secrete. Accordingly, over 20 different types of EECs (named after the letters in the alphabet; e.g. I-cells, L-cells) have been described and well characterised along the mammalian gastrointestinal tract (Gunawardene et al., 2011; Latorre et al., 2016). In birds, several types of EECs (homologous to those in mammals) have been identified and several studies describe their distribution and morphology in the gastrointestinal tract of different species [chick, *Gallus gallus domesticus* (Aksoy and Cinar, 2009; Arcamone et al., 2014; Hiramatsu, 2020; Neglia et al., 2005; Reid and Dunn, 2018; Salvi et al., 1996); ostrich, *Struthio camelus* (Duritis et al., 2013); rufous-collared sparrow, *Zonotrichia capensis subtorquata* (Mendes et al., 2009)]. Compared with mammals and birds, the knowledge of EEC types in other vertebrates is scarce. Available studies suggest that fewer types of EECs are present throughout the gastrointestinal tract in non-mammalian vertebrates, such as reptiles (Burrell et al., 1991; Ferri and Liquori, 1996; Ku et al., 2001; Trandaburu et al., 1999), amphibians (Díaz de Rada et al., 1987; Kostiukevich, 2003; Rovira et al., 1993; Villaro et al., 2001) and fish (Noaillac-Depeyre and Gas, 1982; Pan et al., 2000; Reifel, 1988; Rombout, 1977). For instance, four types of EECs

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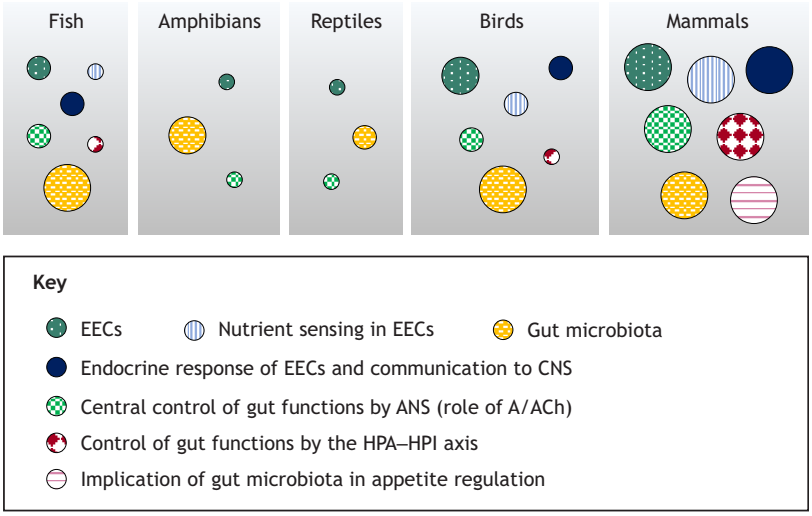

Fig. 1. Illustrative representation of the amount of knowledge (qualitative scale) on the main components of the gut–brain axis available in the different vertebrate groups. Amount of knowledge was determined by the amount of literature on each of the components available on scientific databases (Scopus), and is represented as circles of different sizes. Four circles sizes representing (from smallest to largest circles) very scarce (1–10 publications), little (11–50 publications), some (51–100 publications) and abundant (>100 publications) literature were included in the figure. Sizes were chosen based on the ability to discern between one type and another, and are not strictly proportional to the number of articles. If no literature on a specific category was found, a circle was not included. EECs, enteroendocrine cells; CNS, central nervous system; A, adrenaline; ACh, acetylcholine; ANS, autonomic nervous system; HPA–HPI, hypothalamic–pituitary–adrenal and hypothalamic–pituitary–interrenal axis.

(named I to IV) have been described in the digestive tract of the fish species *Barbus conchonius* (Rombout, 1977).

Nutrient sensing by EECs

EECs represent the first level of integration of the information from the gut lumen, and as such they contain several mechanisms able to detect a wide range of substances present in the lumen, mainly nutrients, but also chemicals, toxins and microorganisms (Dockray, 2003; Furness et al., 2013). Nutrient-sensing mechanisms in the mammalian gut have been extensively studied and have been reviewed by several authors (Gribble and Reimann, 2016; Raka et al., 2019; Rasoamanana et al., 2012). The main receptors and transporters responsible for detecting luminal nutrients in mammals are detailed in Table 1. Chemosensing of nutrients in birds responds, in general, to mechanisms similar to those described in mammals (Niknafs and Roura, 2018; Roura and Foster, 2018). Thus, most of the key mammalian nutrient sensors, including T1R and T2R subfamilies (Cheled-Shoval et al., 2014, 2015; Yoshida et al., 2015), mGluR1 and mGluR4 (Yoshida et al., 2015) and the fatty acid receptors CD36, FFAR4 and FFAR2 (Kawabata et al., 2018; Meslin et al., 2015) are expressed in the chicken's gastrointestinal tract. However, some differences exist between mammalian and avian nutrient sensors, the most important of which are that birds lack the *TAS1R2* gene (encoding T1R2) and only have three *TAS2R* genes (encoding T2R) (Lagerström et al., 2006; Shi and Zhang, 2006).

In fish, most of the available information on gut nutrient sensing is limited to descriptive observations on the presence of different nutrient sensors in the gastrointestinal tract of different species. For instance, Sglt1 and/or its encoding gene (*slc5a1*) have been detected in the gastrointestinal tract of rainbow trout (*Oncorhynchus mykiss*; Geurden et al., 2007; Polakof and Soengas, 2013) and zebrafish (*Danio rerio*; Ye et al., 2019), *tas1r1* mRNAs in the gastrointestinal tract of grass carp (*Ctenopharyngodon idella*; Cai et al., 2018), *tas1r2* in rainbow trout (Polakof and Soengas, 2013), *tas1r3* in rainbow trout (Polakof and Soengas, 2013) and grass carp (Cai et al., 2018), and *gpcr6a* and *casr* in Atlantic salmon (*Salmo salar*; Gomes et al., 2019). Furthermore, expression of mRNAs encoding liver X receptor (LXR), an additional glucosensor (see Glossary) in fish (Otero-Rodiño et al., 2016), has been detected in the proximal and distal intestine of rainbow trout and the pyloric caeca (see Glossary) of Atlantic salmon (Cruz-Garcia et al., 2009). Very recently, a study from our research group reported the presence of mRNAs encoding some key mammalian amino acid receptors (CaSR, GPRC6A, T1r1 and T1r2) in different areas of the rainbow trout gastrointestinal tract, although we did not find transcripts for other receptors (T1r3, mGlur1 and mGlur4). These results led us to suggest that receptors other than those reported in mammals may be involved in luminal sensing of amino acids in fish (J.C., A.M.B., S. Comesaña, M. Conde-Sieira, S. Morais and J.L.S., submitted). Although several studies have reported the presence of nutrient sensors in the fish intestine, only a few studies have characterised the response of these systems to increased levels of nutrients. In this regard, we previously demonstrated that simple sugars, including glucose, galactose and mannose, lead to changes in the intestinal expression levels of glucosensing genes (e.g. increased *slc5a1* and reduced *tas1r2* and *tas1r3* abundance) (Polakof and Soengas, 2013; Polakof et al., 2010). Recently, Ye and co-workers reported that EECs respond to glucose stimulation in an Sglt1-dependent manner, and that the fatty acids palmitate, linoleate and dodecanoate activate a subset of EECs in the zebrafish intestine (Ye et al., 2019). Additionally, recent findings from our research group indicate that *casr*, *gprc6a*, *tas1r1* and *tas1r2* mRNAs are differentially modulated by the intragastric administration of amino acids in the stomach and foregut of rainbow trout (J.C., A.M.B., S. Comesaña, M. Conde-Sieira, S. Morais and J.L.S., submitted), demonstrating the presence of amino acid-sensing mechanisms in the fish gut.

To our knowledge, no specific information on nutrient-sensing mechanisms in the gastrointestinal tract of amphibians and reptiles is available in the literature. Two studies using transcriptome analysis to determine the response of the Burmese python (*Python bivittatus*) to digestion revealed that the expression of some genes encoding typical nutrient sensors in the stomach (e.g. *cd36*) and intestine (e.g. *sglt1*) are significantly dysregulated after feeding (Andrew et al., 2015; Duan et al., 2017). These observations point towards the fact that comparable transporters (and probably receptors) participate in nutrient-sensing mechanisms in the gut of reptiles, but further studies on the specific identification of such transporters and receptors, as well as on their functionality and mechanism of action, are required.

Endocrine signalling by gut hormones

The sensing of luminal nutrients by EECs triggers a cascade of intracellular signalling that ultimately leads to the production and release of signalling molecules, mainly peptide hormones (Sternini et al., 2008). The main peptide hormones released by EECs are ghrelin (see Glossary), cholecystokinin (CCK) (see Glossary),

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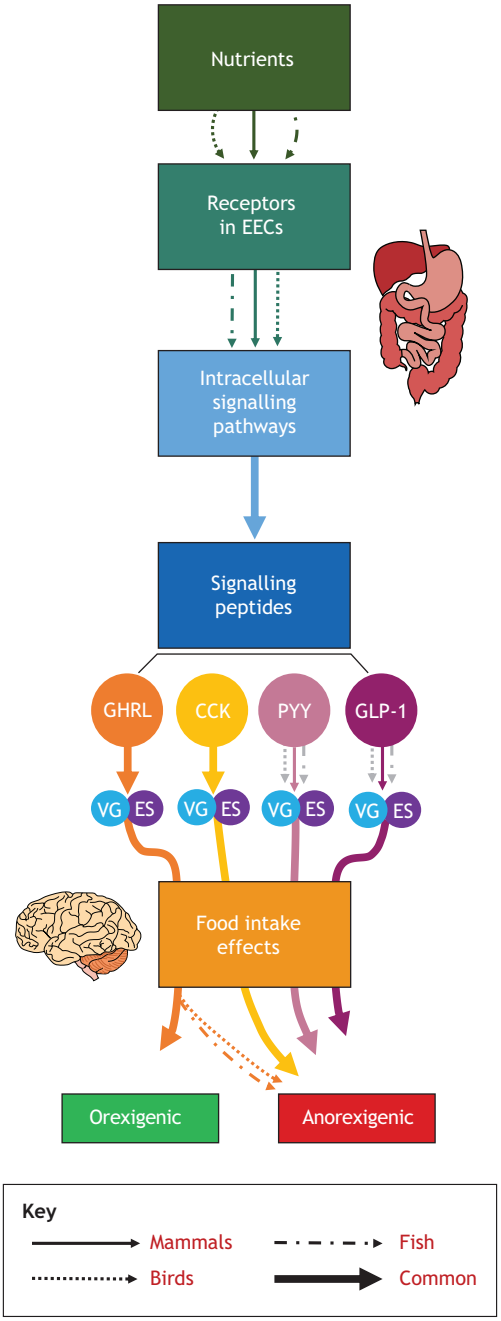

Fig. 2. Schematic model summarising gut-to-brain communication in mammals, birds and fish. When nutrients arrive in the gut lumen, they are detected by receptors in enteroendocrine cells (EECs), which activate an intracellular signalling cascade that ultimately promotes the release of signalling peptides. These peptides transmit information to the central nervous system, either via the vagus nerve (VG) or the endocrine system (ES), in order to regulate food intake. Coloured arrows show known pathways in mammals, birds and fish, and common pathways if they exist; grey arrows indicate unknown pathways. GHRL, ghrelin; CCK, cholecystokinin; PYY, peptide tyrosine tyrosine; GLP-1, glucagon-like peptide-1.

peptide tyrosine tyrosine (PYY) (see Glossary) and glucagon-like peptide-1 (GLP-1) (see Glossary). These hormones, apart from acting locally on neighbouring cells, can enter the circulation and act as classical hormones, or bind to their respective receptors on the vagal afferent terminals that innervate the wall of the gastrointestinal tract, in close proximity to the mucosal epithelium (Brookes et al., 2016).

Table 1. Main nutrient-sensing receptors and transporters found within the mammalian gastrointestinal tract

Nutrient	Receptor/transporter
Carbohydrates/ sugars	Taste receptor 1 family members 2 and 3 (T1R2/ T1R3)
	Sodium-coupled glucose transporter 1 (SGLT1)
Proteins/amino acids	T1R1/T1R3 heterodimer
	Calcium-sensing receptor (CaSR)
	G-protein-coupled receptor family C group 6 member A (GPRC6A)
	G-protein-coupled receptor 92/93 (GPR92/93)
	Metabotropic glutamate receptors (mGluR)
	Proton-dependent epithelial peptide transporter 1 (PEPT1 or SLC15A1)
	Neutral amino acid transporter 1 (BOAT1 or SLC6A19)
Lipids/fatty acids	Fatty acid translocase or cluster of differentiation 36 (CD36)
	Fatty acid transport protein 4 (FATP4)
	Free fatty acid receptor 4 (FFAR4 or GPR120)
	Free fatty acid receptor 1 (FFAR1 or GPR40)
	Free fatty acid receptor 3 (FFAR3 or GPR41)
	Free fatty acid receptor 2 (FFAR2 or GPR43)
	GPR119

Vagal afferent pathways convey stimuli generated by EECs to the CNS, specifically to the nucleus of the solitary tract (NTS) in the brainstem, which receives and distributes the information to other central areas, the most important of which is the hypothalamus. Two main sets of neurons with opposite metabolic effects reside in the hypothalamic arcuate nucleus: the neuropeptide Y (NPY) (see Glossary) and agouti-related protein (AgRP) neurons (see Glossary), which stimulate food intake (orexigenic) (see Glossary) and reduce energy expenditure, and the proopiomelanocortin (POMC) (see Glossary) and cocaine- and amphetamine-regulated transcript (CART) neurons (see Glossary) that inhibit food intake (anorexigenic) (see Glossary) and increase energy expenditure. In response to the information from the NTS or to the direct action of local or circulating hormones, the expression of these two sets of neuropeptides, together with that of other important brain appetite-regulatory neuropeptides (e.g. orexin) (see Glossary), is differentially regulated. This way, stimuli generated by EEC-secreted hormones can reach the CNS, influencing a wide range of physiological processes governed by central circuitries, including food intake, intestinal motility and gastric and intestinal secretion of both digestive enzymes and hormones (Mayer, 2011; Raybould, 2010), among many others (Fig. 2). Below we provide some examples of EEC–CNS communication that involve each of the major gut hormones in mammals and the available knowledge on these proteins in other vertebrate groups.

Ghrelin

Ghrelin-producing cells, known as X/A-cells in rodents and P/D1-cells in humans, are predominantly located in the stomach, although they are scattered in all regions of the gastrointestinal tract, at least in rodents (Sakata and Sakai, 2010). These cells exist as both open- and closed-type in the intestine (Sakata et al., 2002); however, all ghrelin-secreting cells in the stomach are closed-type, which implies that ghrelin secretion is not likely to be under direct control from luminal content, but is instead determined by absorbed nutrients, nerves and hormonal regulation (Stengel and Taché, 2009). Unlike the majority of gut hormones, which are secreted post-prandially, ghrelin secretion in mammals increases in the pre-prandial and fasting states, when it promotes food intake, and falls rapidly after a meal (Cummings et al.,

2001; Tschöp et al., 2000). Although a wide range of functions have been attributed to ghrelin (Ibrahim Abdalla, 2015; Pradhan et al., 2013), its role in food intake is the most-studied one. Peripherally administered ghrelin has been reported to increase appetite in almost all vertebrate groups studied so far, including mammals (human: Klok et al., 2007; rat, *Rattus norvegicus*: Wren et al., 2001), amphibians (bullfrog, *Rana catesbeiana*: Shimizu et al., 2014) and most fish species assessed (goldfish, *Carassius auratus*: Blanco et al., 2017; Matsuda et al., 2006a,b; Unniappan et al., 2004; cavefish, *Astyanax fasciatus mexicanus*: Penney and Volkoff, 2014). However, a few studies in fish reported an anorexigenic action of ghrelin when administered peripherally (rainbow trout: Jönsson et al., 2010; channel catfish, *Ictalurus punctatus*: Schroeter et al., 2015), suggesting that the appetite-regulating action of this hormone in this vertebrate group is species specific. In birds, results are also contradictory, and both orexigenic (Japanese quail, *Coturnix japonica*: Shousha et al., 2005) and anorexigenic (chicken: Geelissen et al., 2006) effects have been described for ghrelin upon intraperitoneal treatment. At least in mammals, the effects of ghrelin on food intake are mediated in large part by the hypothalamus (Klok et al., 2007). Some evidence suggests that a small amount of ghrelin is synthesised locally in some brain regions, such as the hypothalamus, and thus might be able to directly affect the various hypothalamic nuclei (Cabral et al., 2017). Gut-derived ghrelin is proposed to act on the CNS by two different pathways: (1) by being transported through circulation, crossing the blood–brain barrier and binding to specific receptors in the hypothalamus (Rhea et al., 2018) or (2) by activating specific receptors located at peripheral endings of the vagus nerve (Date et al., 2002). The mechanisms underlying the connection between gut-derived ghrelin and the CNS are not entirely known in non-mammalian vertebrates. Some fish studies have reported changes in the mRNA abundance of appetite-regulating peptides in the brain in response to peripheral administration of ghrelin, supporting the existence of a gut–brain axis for mediating ghrelin action on food intake. Thus, intraperitoneal injection of ghrelin increases the expression of mRNAs encoding the appetite-stimulatory hypothalamic neuropeptide orexin in the hypothalamus of goldfish (Nisembaum et al., 2014) and in the whole brain of cavefish (Penney and Volkoff, 2014), suggesting that this neuropeptide might mediate the orexigenic action of ghrelin. However, no effects of intraperitoneal ghrelin on mRNA abundance were observed for hypothalamic *npy* in goldfish (Miura et al., 2006; Nisembaum et al., 2014), for hypothalamic *npy* and *pomca* in channel catfish (Schroeter et al., 2015), and for whole brain *cartpt* and *cck* in cavefish (Penney and Volkoff, 2014). In addition, a study in goldfish demonstrated that the orexigenic action of peripherally administered ghrelin is abolished by pre-treatment with the neurotoxin capsaicin, which destroys the primary sensory (vagal and splanchnic) afferents (Matsuda et al., 2006b). This suggests that the pathway mediating ghrelin action on food intake is likely to be common from fish through to humans, although further studies are required to confirm such a hypothesis.

CCK

CCK is mainly secreted by I-cells in the upper small intestine (duodenum and jejunum) and by CCK neurons in response to the ingestion of proteins and lipids (Rehfeld, 2017). In mammals, the postprandial release of CCK entails some local, peripheral physiological actions, exerted mainly through activation of CCK_1 receptors in vagal afferent terminals (Bucinskaite et al., 2000). These include the stimulation of gallbladder contraction and relaxation of the sphincter of Oddi in order to allow bile to flow into the duodenum, the delay of gastric emptying, and the stimulation of gut motility, among others (Miyasaka and Funakoshi, 2003). Some or most of these effects of CCK have also been described in non-mammalian vertebrates, including birds (chicken: Martínez et al., 1993; and see review by Wang and Cui, 2007), amphibians (see review by Vigna, 1983) and fish (see review by Volkoff et al., 2005). Apart from its peripheral actions, mammalian CCK has a potent anorexigenic role, which is also exerted through its effects on CCK_1 receptors on vagal afferent nerves, providing negative feedback to the CNS to limit food intake (Peters et al., 2006). The satiety effects of peripheral CCK via vagal mediation have been also demonstrated in birds, in a study reporting that intraperitoneal administration of CCK suppresses food intake in control but not in vagotomised chickens (Covasa and Forbes, 1994). In fish, CCK reduces food intake in different species when administered intraperitoneally (goldfish: Blanco et al., 2017; Himick and Peter, 1994; cavefish: Penney and Volkoff, 2014; coho salmon, *Oncorhynchus kisutch*: White et al., 2016; Siberian sturgeon, *Acipenser baerii*: Zhang et al., 2017). Such an inhibitory effect is blocked by the co-administration of capsaicin in goldfish (Kang et al., 2010), suggesting a vagus nerve-mediated regulation of CCK satiety effects in fish, as in birds and mammals. In favour of the existence of a gut–brain connection for CCK in fish, Zhang and co-workers reported that intraperitoneal administration of CCK in Siberian sturgeon alters the brain expression of appetite-regulating peptides, i.e. it increases mRNA levels of *npy*, *cartpt* and nucleobindin 2 (*nucb2*) (Zhang et al., 2017). Similarly, intraperitoneally administered CCK results in decreased abundance of *apelin* mRNA in the whole brain of cavefish (Penney and Volkoff, 2014).

PYY

PYY is secreted by L-cells, which are most abundant in the distal small intestine (jejunum and ileum) and large intestine (Spreckley and Murphy, 2015). Secretion occurs especially in response to feeding with lipids, but also upon carbohydrate and protein ingestion (Steinert et al., 2017). Two endogenous molecular forms of PYY have been identified, PYY1–36 and PYY3–36, with the latter being the predominant form in circulation (Grandt et al., 1994). The main physiological action of PYY is its effect on appetite regulation. Intraperitoneal administration of PYY has been reported to significantly reduce food intake in rodents and humans (Batterham et al., 2002; Chelikani et al., 2007), as well as in different fish species (goldfish: Blanco et al., 2017; Gonzalez and Unniappan, 2010; Gonzalez and Unniappan, 2016; grass carp *Ctenopharyngodon idellus*: Chen et al., 2013). Likewise, PYY decreases appetite in chicks when administered intravenously (Aoki et al., 2017). At least in mammals, the satiety effects of PYY are largely mediated by direct action on the hypothalamus. Thus, circulating PYY reaches the hypothalamus via the semi-permeable capillaries of the median eminence (see Glossary) to bind Y2 receptors in NPY and POMC neurons of the arcuate nucleus, inhibiting the former and activating the latter (Batterham et al., 2002; Ghamari-Langroudi et al., 2005). Y2 receptors are also present on vagal afferents (Koda et al., 2005), raising the possibility that PYY also exerts its feeding effects by vagal activation. However, the importance of the vagus nerve in mediating the effects of PYY on feeding is under discussion. Whereas two independent groups have reported the abolishment of the anorectic effects of peripherally administered PYY3–36 in vagotomised rats (Abbott et al., 2005; Koda et al., 2005), neither vagotomy (Halatchev and Cone, 2005) nor systemic pre-treatment with capsaicin (Talsania et al., 2005) cancelled PYY3–36 satiety effects in mice. The mechanisms of action underlying the anorectic role of PYY in non-mammalian vertebrates are largely unknown. In fish, a study in

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channel catfish reported that hypothalamic mRNA levels of *npy* and *pomc* are not altered by the intraperitoneal administration of PYY (Schroeter et al., 2015), suggesting that a different mechanism mediates PYY's satiety role in fish compared with mammals. Nevertheless, whether peripheral PYY acts directly on the brain or via vagal stimulation to reduce appetite in non-mammals is yet to be investigated. In addition to appetite, PYY increases energy expenditure, slows gastric emptying (thereby increasing the efficiency of digestion and nutrient absorption) and regulates glucose homeostasis by modulating pancreatic islet function in mammals (Karra et al., 2009; Spreckley and Murphy, 2015). Unfortunately, studies regarding the role of PYY are not available in vertebrates other than fish.

GLP-1

As is the case for PYY, L-cells are responsible for producing and secreting GLP-1 in mammals (Spreckley and Murphy, 2015). This hormone is abundantly secreted in response to the ingestion of carbohydrates and lipids, and less pronounced in response to proteins (Steinert et al., 2017). In mammals, GLP-1 is well known for its role as an incretin hormone, i.e. it contributes, together with the gastric inhibitory peptide (GIP), to postprandial glucose clearance through the stimulation of insulin secretion from the pancreatic β-cells (Holst, 2007). An insulinotropic activity for GLP-1 has also been suggested in birds (at least in chickens), although such activity seems to be mediated by the modulation of somatostatin production from pancreatic δ-cells rather than by direct β-cell stimulation (Watanabe et al., 2014). In fish, on the contrary, available evidence argues against an incretin function for GLP-1 (Mommsen, 2000). Besides this role, GLP-1 has been shown to reduce gastric emptying via vagal nervous activity (Imeryüz et al., 1997) and to reduce food intake in mammals (Dailey and Moran, 2013). Due to the short half-life (approximately 2 min) of GLP-1 in mammals, its effects on food intake are likely to be mediated (at least in part) by a paracrine signalling mechanism near the site of release, which involves the activation of the vagus nerve, as demonstrated using various lesion models (Krieger et al., 2015). However, it has been proposed that circulating GLP-1 may also elicit its effects on food intake by directly stimulating central anorexigenic pathways, particularly POMC- and CART-expressing neurons in the hypothalamic arcuate nucleus (Secher et al., 2014). In non-mammalian vertebrates, a suppressive role for peripherally administered GLP-1 on food intake has also been described in birds (Japanese quail: Shousha et al., 2007) and fish (goldfish: Blanco et al., 2017; coho salmon: White et al., 2016). The mechanism of action underlying such satiety effect in birds remains unexplored. In fish, intraperitoneal administration of GLP-1 in rainbow trout results in increased mRNA abundance of hypothalamic *pomca1* and hindbrain *cartpt* (Polakof et al., 2011), suggesting that similar endocrine pathways to those described in mammals might mediate GLP-1's satiety effects in this vertebrate group. However, Schroeter and co-workers detected no changes in the mRNA abundance of *npy* and *pomc* in the hypothalamus of another fish species (channel catfish) in response to intraperitoneally injected GLP-1 (Schroeter et al., 2015). In addition, using capsaicin, it was reported that at least part of the actions of GLP-1 on glucose homeostasis in rainbow trout are mediated by vagal and splanchnic afferents (Polakof et al., 2011). Whether the vagus nerve mediates the effects of GLP-1 on food intake in fish is yet to be investigated, but previous observations by Polakof and co-workers in rainbow trout (Polakof et al., 2011) argue in favour of such a hypothesis.

Central regulation of gut functions

The gastrointestinal tract differs from other peripheral organs because it has an extensive intrinsic nervous system, the ENS. The ENS is present in all vertebrate groups, including mammals (Spencer and Hu, 2020), birds (Heanue et al., 2016), reptiles (Junquera et al., 2001), amphibians (Sundqvist and Holmgren, 2004) and fish (Ganz, 2018; Olsson, 2010). The ENS controls gastrointestinal tract functions even when completely separated from the CNS (Furness, 2016); however, it is not completely autonomous as the brain communicates with the gastrointestinal tract through several parallel pathways (Fig. 3). The main pathway through which the brain sends signals to the gastrointestinal tract is via the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) (see Glossary), whose responses are governed by several hypothalamic and hindbrain nuclei and (sub)cortical regions (especially the amygdala), which exert a modulatory influence on them (Weltens et al., 2018). Whereas the ANS represents the main neural component of the brain-to-gut communication, the hypothalamic–pituitary–adrenal (HPA) axis [or its hypothalamic–pituitary–interrenal (HPI) equivalent in reptiles, amphibians and fish] plays the main endocrine role in such interactions. Corticotropin-releasing factor (CRF), secreted by the hypothalamus, is the main hormone governing this axis, and has been described in all vertebrates groups, from fish to mammals (see review by Cardoso et al., 2016).

Whereas the gut-to-brain connection within the gut–brain axis has a notorious and direct influence on food intake, brain-to-gut pathways are involved with modulating gastrointestinal processes that take place after the intake of a meal rather than food intake *per*

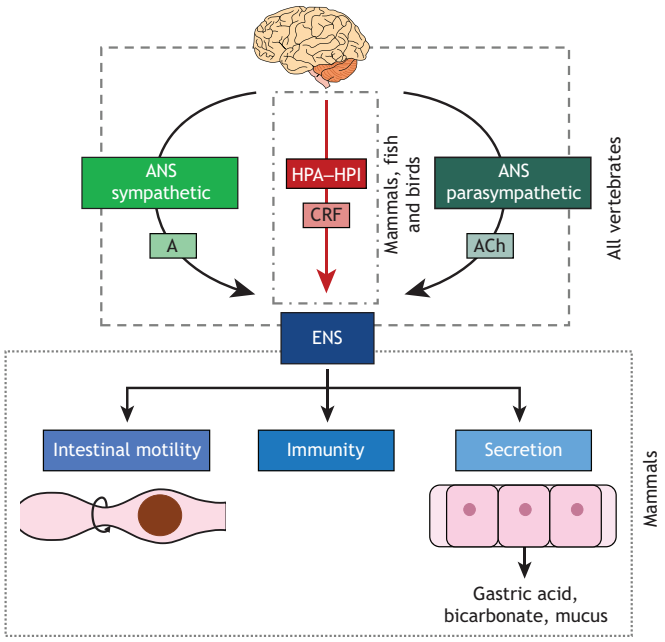

Fig. 3. Brain-to-gut communication by the autonomic nervous system and the HPA–HPI axis in vertebrates. The vertebrate brain communicates with the gastrointestinal tract through several parallel pathways, the most important of which are the sympathetic and parasympathetic branches of the autonomic nervous system (ANS), whose main neurotransmitters are adrenaline (A) and acetylcholine (ACh), respectively, and the hypothalamic–pituitary–adrenal and hypothalamic–pituitary–interrenal axis (HPA–HPI), whose main effector is corticotropin-releasing factor (CRF). These systems communicate with the enteric nervous system (ENS), affecting intestinal motility, secretory processes and immune functions.

se. Two of the most important of these processes are gut motility and secretion. Gut motility is necessary for food transport and processing, and is the result of the depolarisation (contraction) and repolarisation (relaxation) of smooth muscle (Olsson and Holmgren, 2011). Secretion is essential for food processing in the gastrointestinal tract and occurs in different places, including the salivary glands, gastric glands and mucous glands along the intestine and pancreas (or scattered pancreatic cells in vertebrates without a defined pancreas) (Schubert and Shamburek, 1990; Singh and Webster, 1978).

The regulation of gut motility and secretion by the ANS has been well documented in mammals. Within this regulation, the sympathetic and parasympathetic efferent branches connect emotional arousal and central autonomic brain circuits with the ENS, which in turn innervates visceral smooth muscles and other end-organ structures that affect gut motility (Weltens et al., 2018). In general terms, the sympathetic innervation has an overall inhibitory effect on gut motility in mammals, delaying transit time of food along the gastrointestinal tract, whereas the opposite effect is exerted by the parasympathetic branch (Browning and Travagli, 2014; Mayer, 2011). In non-mammals, knowledge about the effects of sympathetic or parasympathetic pathways on intestinal motility is mostly restricted to the effect of their neurotransmitters rather than on their activation. Thus, regarding sympathetic regulation of gastrointestinal tract motility, it has been reported that adrenaline inhibits motility in the intestine of birds (Ogino et al., 2016; Saba and Arowolo, 2007), reptiles (Knight and Burnstock, 1999), amphibians (Murphy and Campbell, 1992) and fish (Kitazawa et al., 1990; Venugopalan et al., 1994). Likewise, in non-mammals, the parasympathetic pathway appears to exert an excitatory action towards motility comparable to that exerted in mammals, as supported by the excitatory effects of acetylcholine in the gastrointestinal tract of reptiles (Holmberg et al., 2002; Knight and Burnstock, 1999), amphibians (Shonnard and Sanders, 1990) and fish (Kitazawa et al., 1990; Mensah et al., 2018). Regarding secretion, it is well known in mammals that the ANS controls this process either directly (mainly via parasympathetic pathways) or indirectly by controlling blood flow (mainly via sympathetic pathways) (Browning and Travagli, 2014). The most studied secretory process within the gastrointestinal tract is the secretion of gastric acid in the stomach. This secretion is under parasympathetic control in mammals, as demonstrated by direct stimulation of the vagus nerve, acetylcholine treatment or absence of secretion after vagotomy (Browning and Travagli, 2014). Some evidence supports a similar role for the parasympathetic system in amphibians (Fong et al., 1991; Ruiz and Michelangeli, 1984) and fish (Holstein and Cederberg, 1980). Apart from the available knowledge on the role of the ANS in gastric acid secretion, our understanding of secretion in non-mammals is almost restricted to studies on the effects of neurotransmitters. For instance, in amphibians, it has been reported that noradrenaline inhibits mucous secretion from the stomach of amphibians *in vitro* (Keogh et al., 1997) and that acetylcholine stimulates intestinal mucus secretion in the frog (Slaughter and Aiello, 1982). In birds, pancreatic secretion is stimulated by acetylcholine (Meacham and Johnson, 2003; Murai et al., 2000; Wang et al., 2009) and inhibited by adrenaline (Salido et al., 1985). Similarly, in fish, pancreatic secretion is enhanced by cholinergic agents and inhibited by adrenergic drugs (Milgram et al., 1991). However, it is important to mention that acetylcholine is not restricted to the ANS but it is also present in the ENS; thus conclusions on the effects of parasympathetic innervation on intestinal motility and secretion derived only from studies testing the effects of neurotransmitters should be made with care.

Like the ANS, the HPA–HPI axis, a central hormonal response system to stress, is an important modulator of gastrointestinal tract functions. At least in mammals, among other effects, stress increases the sympathetic tone and decreases the parasympathetic tone in the ANS. These stress-affecting systems have an impact on the gastrointestinal tract, influencing motility and secretion, immune function and microbiota composition and function (Niccolai et al., 2019; Stengel and Taché, 2018). In addition, CRF has been shown to exert direct effects on the gastrointestinal tract, independent of the HPA axis. By binding to the CRF receptor 1 (CRF-R1) in the gut, CRF activates colonic myenteric neurons and mucosal cells that secrete serotonin and mucus, and enhances mucosal permeability and propulsive motor functions in rodents and humans, among other functions (Tache et al., 2018; Weltens et al., 2018). In non-mammalian vertebrates, there is little research on the communication between the HPA–HPI axis and the gastrointestinal tract (Williams et al., 2020). However, in a few species of birds (e.g. yellow-legged gull, *Larus michahellis*: Noguera et al., 2018) and fish (rainbow trout: Rosengren et al., 2018) it has been reported that hormonal manipulation of the HPA–HPI axis can significantly alter intestinal microbiota. However, it is difficult to make generalisations given the small number of species assessed, as, for instance, no effects of HPI manipulation were observed in the zebrafish gastrointestinal tract (Brady et al., 2017).

The gut microbiota and its implications in food intake control

Every animal is a host for a complex community of microorganisms present from the skin surface to the gut, containing thousands of species from all taxonomic domains (Bacteria, Archaea and Eukarya) (Hird, 2017). Bacteria, mainly anaerobic species, dominate gut microbiota above other organisms, and of the 100 trillion bacteria in the human body, 80% are in the digestive tract (Wang and Wang, 2016). The composition of the intestinal microbiota differs among vertebrate groups (Bercik et al., 2012), the gut microbiota of terrestrial mammals being the most widely investigated of vertebrate-hosted microbial communities. Gut microbiota exhibit a mutually beneficial relationship with the host because they produce metabolites that are involved in the modulation of host physiological functions, thereby contributing to the host's fitness (Huang et al., 2018; Nicholson et al., 2012). Studies from the last decade have demonstrated that the gut microbiota, apart from modulating other processes such as the immune response, is involved in the control of energy homeostasis by regulating feeding and digestive and metabolic processes (Butt and Volkoff, 2019). Very recently it has also been demonstrated that the gut microbiome can influence host diet selection (Trevelline and Kohl, 2020 preprint). The modulation of food intake and appetite by the gut microbiota occurs mainly through microbial influence on satiety and reward pathways and on the production of toxins that alter mood (Alcock et al., 2014; Norris et al., 2013). To modulate satiety and reward pathways, microbial metabolites can activate EECs, triggering the release of gut peptides, which leads to a modulation of food intake as described in earlier sections (Huang et al., 2018; Martin et al., 2018). Alternatively, they can directly act on vagus nerve afferent terminals located in the lamina propria, also affecting central appetite-regulatory centres as described above (Cryan and O'Mahony, 2011; Kim and de La Serre, 2018) (Fig. 4).

The most important microbial metabolites are short-chain fatty acids (SCFAs) or fatty acids with a chain length of between two and six carbon atoms, the most important of which are butyrate, acetate and propionate. SCFAs can be present in small quantities in the diet but their main source is bacterial anaerobic fermentation of non-digestible carbohydrates. In mammals, SCFAs are known to play a

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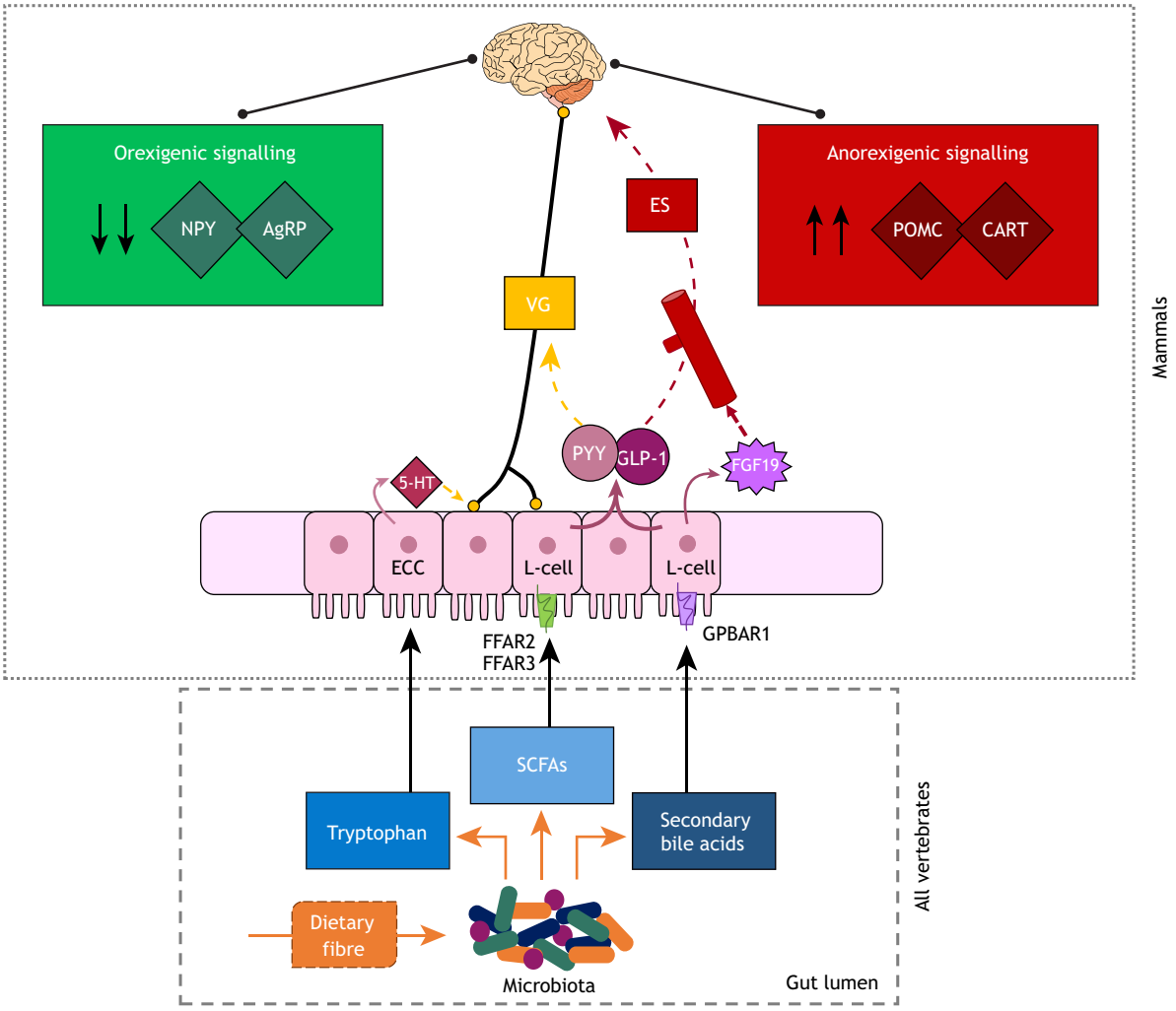

Fig. 4. Schematic representation of the role of gut microbiota in food intake regulation via the microbiota gut–brain axis in vertebrates. Anaerobic fermentation of dietary fibre by gut microbiota produces metabolites [short-chain fatty acids (SCFAs), bile acids and tryptophan, among others] that act on intestinal cells, mainly enteroendocrine L-cells and enterochromaffin cells (ECC), stimulating the production of gut hormones [e.g. peptide tyrosine tyrosine (PYY), glucagon-like peptide-1 (GLP-1) and fibroblast growth factor 19 (FGF19)] and neurotransmitters (serotonin, 5-HT), respectively. Via the vagus nerve and/or the endocrine system, these molecules can modulate the levels of appetite-regulating neuropeptides in the nervous central system, mainly the orexigens neuropeptide Y (NPY) and agouti-related protein (AgRP) or the anorexigens proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) in the hypothalamus, thus stimulating or inhibiting food intake, respectively. Coloured arrows show known pathways in mammals or all vertebrates, if they exist. Grey arrows indicate unknown pathways. FFAR2 and FFAR3, free fatty acid receptors 2 and 3; GPBAR1, protein-coupled bile acid receptor 1; VG, vagus nerve; ES, endocrine system.

critical role in food intake regulation (Huang et al., 2018; Martin et al., 2018). Through binding to FFAR2 and FFAR3 in L-cells, these metabolites stimulate the release of satiety peptides, such as PYY and GLP-1 (see review by Sleeth et al., 2010), which, as mentioned above, ultimately inhibit food intake. Also arguing for a role of the gut microbiota in food intake regulation in mammals, it has been reported that germ-free mice, which present poor levels of SCFAs due to the absence of microbiota, show increased food intake to compensate for reduced energy harvest (Tremaroli and Bäckhed, 2012). In fish, several studies have reported the production of SCFAs in the gastrointestinal tract, with the highest levels occurring in the distal intestine (Tran et al., 2020). In addition, in contrast to what it is observed in mammals, carnivorous fish were shown to have relatively higher concentrations of SCFAs than herbivorous or omnivorous species (Tran et al., 2020). However, there are no studies available on the role of gut microbiota-derived SCFAs in appetite regulation either in fish or in birds, reptiles or amphibians. Only one functional study in sea bass by Estensoro and co-workers demonstrated that butyrate improves or even reverses the detrimental effects of consuming a plant-based diet, which includes the up-regulation of inflammatory markers and high presence of granulocytes and lymphocytes in the submucosa (Estensoro et al., 2016).

Other important bacterial metabolites are the secondary bile acids and tryptophan. A percentage of the bile acids that are produced in the liver are transformed into secondary bile acids by gut microbiota (Nicholson et al., 2012). In mammals, these bile acids can promote the release of GLP-1 by the activation of protein-coupled bile acid receptors in L-cells, thus affecting food intake (Brighton et al., 2015). Moreover, bile acids activate the ileal expression of the nuclear receptor farnesoid X (FXR) in rodents, leading to the production of fibroblast growth factor 19 (FGF19), which can enter the systemic circulation and reach the hypothalamus to block AgRP and NPY neuron activity, affecting food intake (Marcelin et al.,

2014; Ryan et al., 2013). Lastly, tryptophan, an essential amino acid precursor of many metabolites involved in gut–brain signalling, such as the neurotransmitter serotonin (5-HT), plays a central role in gastric motility-mediated appetite regulation in mammals (Cussotto et al., 2018; Martin et al., 2018). As in the case of SCFAs, the available information on how bile acids and tryptophan are involved in appetite regulation is based only on mammalian studies; similar data are lacking in other vertebrates.

Conclusions

The gut–brain axis has been extensively studied in recent years in mammals due to its importance in the regulation of gastrointestinal tract functions and for the involvement of the gastrointestinal tract and gut microbiota in the regulation of different behaviours, including food intake (Parker et al., 2020). In contrast, knowledge on the function of the gut–brain axis in non-mammalian vertebrates is very scarce, and often derives from a single study or a group of studies carried out in a single species; thus, it may not be representative for the entire group. Despite this fact, some general observations can be made. First, EECs are clearly a component of the gut–brain axis in all vertebrate groups and represent the first level of integration of the information from the gut lumen, thus being in charge of sensing the luminal content and responding with the release of signalling molecules (mainly peptide hormones) that will transmit information to the CNS. These cells appear to respond to the luminal presence of nutrients in a comparable way between mammals and birds with a few exceptions, such as the lack of TAS1R2 and the species-specific role of ghrelin on food intake in birds. In fish, more differences in the response of EECs to nutrients seem to exist when compared with mammals and birds, such as the different activation profile of nutrient receptors by different nutrients, the non-incretin role of GLP-1 or the contradictory effects of ghrelin on food intake, among others. Considering that fish are phylogenetically older than birds and mammals, it is tempting to suggest that these differences might relate to the appearance of novel functions and mechanisms during evolution. This hypothesis, however, would require the collection of more information in amphibians and reptiles, which are phylogenetically placed between fish and birds, and mammals, and for which almost no information is available in the literature. Second, the connection from the brain to the gastrointestinal tract is governed by the HPA–HPI axis and the sympathetic and parasympathetic branches of the ANS in all vertebrate groups, and appears to respond to similar mechanisms. Thus, for instance, adrenaline (main neurotransmitter of the sympathetic system) and acetylcholine (main neurotransmitter of the parasympathetic system) appear to inhibit and stimulate, respectively, gut motility in all vertebrates.

Although some general observations on the gut–brain axis in vertebrates can be drawn, several gaps in knowledge can be identified in non-mammalian vertebrates. For instance, the mechanisms of action underlying the orexigenic/anorectic role of gut hormones are basically unknown in non-mammals, especially in amphibians and reptiles. In addition, it is not possible to make any generalisation regarding the central control of secretory processes occurring within the gastrointestinal tract, as the number of studies in non-mammalian vertebrates is very small and restricted to a few species of amphibians, fish and birds. Concerning the gut microbiota, there is ample evidence for its composition in vertebrates (Williams et al., 2020); however, the role of signalling molecules from gut microbiota (such as SCFAs) in the modulation of central functions in the host has only been assessed in mammals. This highlights some of the many important gaps in knowledge regarding the gut–brain axis in non-mammalian vertebrates. Hopefully, research in the coming years will allow us to draw a better picture of how the gut–brain axis has been adapted over the course of vertebrate evolution.

Competing interests

The authors declare no competing or financial interests.

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