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Supplementary information

Mechanistic insights into the liver–brain axis during chronic liver disease

In the format provided by the authors and unedited

Hormone or hepatokine	Site of release	Influence on behaviour and physiology in health (unless stated otherwise)	Mechanisms	Changes in levels in chronic liver disease
GLP1	Gastrointestinal tract (L cells)	Appetite↓[1]	Vagal afferent activity↑[1,2]	↓MASLD and MASH[3,4] ↑Patients with post-hepatectomy liver failure[5]
		Gastric emptying and secretion↓[6,7]	Vagal afferent and efferent activity↑[2,6-8]	
		Blood glucose↓[2,9,10]	Hepatic vagal afferent activity↑[11] Hepatic insulin sensitivity↑[12] Multiple direct effects on pancreatic α-cells, β-cells, and δ-cells[13-15]	
		Hepatic triglycerides↑	PI3K signalling↑ in hepatocytes[16]	
GLP2[a]	Gastrointestinal tract (L cells)	Intestinal growth following resection↑[17]	NTS activity↑ through vagal afferent pathway[18]	↓MASLD and MASH (follows GLP1)[19] ↓Sclerosing cholangitis[20]
Oxyntomodulin[b]	Gastrointestinal tract (L cells)	Appetite↓[21-23]	Activation of GLP1 receptors and increased αMSH release from arcuate nucleus neurons[22]	No significant changes in MASLD[24]
		Energy expenditure[25]	Unknown	
		Liver circadian rhythm[26]	Hepatocyte *Per1* and *Per2* expression through glucagon receptor activation[26]	
		Blood glucose↓[27,28]	Activation of hepatocyte glucagon receptors[27] Direct effect on pancreatic β-cells[29]	
CCK8	Gastrointestinal tract (I cells)	Appetite↓[30]	Activation of vagal afferent signalling[31,32] and direct central mechanisms[33]	↑MASH[34]
		Liver inflammation, fibrosis, and steatosis↑[34]	Unspecified	
		Blood glucose↓[35,36]	Gut→brain→liver vagovagal loop[35] Glucose-dependent insulin release from β-cells↑[37,38]	
		Gastric emptying↓[36]	Vagal afferent signalling↑[39] and enteric nervous system activity↑[40]	

Ghrelin[c]	Stomach (P cells)	Food-related memory↑[41]	GHSR signalling on gut-innervating vagal afferents[41]	↓MASLD[42-44]
		Gastric emptying↑[45]	Regulation of vagal efferent signalling[46] and enteric nervous system function[45]	
		Hepatic glucose production↑	Gut-innervating vagal afferent signalling in the NTS↑[47] Direct activation of arcuate nucleus AgRP neurons[48]	
		Hepatic lipogenesis↑[49] and lipid accumulation↑[44]	Direct effects on the brain[49] Direct effects on hepatocytes[50,51]	
		Hepatocyte cell death↓[42]	↓TNF-induced hepatocyte apoptosis, autophagy, and pyroptosis[42]	
		Liver fibrosis↓[52,53]	TGFβ1–Smad3, NF-κB signalling↓[52] Autophagy↓[42]	
		Appetite↑[54,55]	Vagal afferent activity↓[56] LEAP2 expression in the liver↓[57] Desensitization of vagal afferents to gastric distension[58,59] Direct activation of hypothalamic neurons[48,60,61]	
		Growth hormone secretion↑[62]	Activation of hypothalamic arcuate nucleus neurons and the pituitary	
PYY	Gastrointestinal tract (L cells)	Appetite↓[63-66]	Vagal afferent activity↑[67]	↑(Decompensated) cirrhosis[68] ↓Patients with hepatitis B virus[69]
		Gastric emptying↓[66,70]	Vagal efferent acetylcholine release onto enteric nervous system neurons[71] Vagal afferent activity↑[67]	
		Glucose tolerance↑[72]	Hepatoportal GLP1 levels↑[72]	
GIP	Gastrointestinal tract (K cells)	Glucose tolerance↑[10,73] or no change[74]	Insulin release↑[73]	↑MASLD[75]
		Appetite↓[76] or no consistent change[77,78]; conflicting results[79]	Direct effect on GABAergic neurons in the brain[73,80]	
		Proximal stomach emptying↑[78] with no overall effect on gastric emptying[74,81]	Unspecified	

FGF21[d]	Hepatocytes	Modulates energy intake, depending on energy state and particular macronutrient: food intake under fed state↓[82]; sucrose preference↓↑ [83,84] dependent on metabolic state[84]; protein preference↑ [84]	Activation of PVN [82,83] Activation of ventromedial hypothalamus [85]	↑MASLD and MASH[86,87] (potential regional desensitization)
		HPA axis activity↑[88-91]	Hypothalamic CRH↑[92]	
		Glucose homeostasis during starvation [93]	Hepatic expression of PGC1α[93] Fatty acid oxidation↑ Hepatic gluconeogenesis↑[93] mediated by hypothalamic CRH [91]	
		Glucose homeostasis during refeeding and overfeeding↑	Insulin-mediated glucose uptake↑[94]	
		Sympathetic outflow↑ and brown adipose tissue thermogenesis↑[92]	CRH expression in the PVN↑[92]	
GDF15	Hepatocytes	Appetite↓[95,96]	AP and NTS CCK neuron activity↑→ parabrachial nucleus and central amygdala activity↑[95-98]	↑MASLD[99,100] and cirrhosis[101]
		Nausea and/or emesis↑[102,103]		
		Energy expenditure maintenance during calorie restriction[104]	GFRAL–β-adrenergic-dependent signalling axis ↑Fatty acid oxidation and calcium futile cycling in skeletal muscle[104]	
		Hepatic triglyceride export↑[105]	Hepatic sympathetic outflow via β-adrenergic signaling↑[105]	
Fetuin A	Hepatocytes	Lipogenesis↑[106]	Stimulation of fatty acid incorporation into monoglycerides, diglycerides and triglycerides[107]	↑MASLD[108] ↓Patients with cirrhosis and Wilson disease[109]
		Anti-inflammatory responses↓ (during acute inflammation)[110]	Inhibition of TNF production and PAMP-induced HMGB1	

			release by innate immune cells[111]	
		Pro-inflammatory responses↑ and impairs the response to insulin (during chronic inflammation)[112]	Endogenous ligand for TLR4 in adipocytes that triggers lipid-induced inflammation, resulting in insulin resistance[113,114] via the NF-κB pathway[115]	
		Clearance or uptake of glucose from blood and modulation of insulin sensitivity[116]	Phosphorylation status of insulin receptor Alteration of lipid metabolism[116]	
ANGPTL8	Hepatocytes	Regulates lipid metabolism[117]	NPY signaling in the dorsomedial hypothalamus[118]	↑MASLD[119] and cirrhosis[120]
		Food intake↓[117,118]		
		Accelerate MASLD-associated liver fibrosis[121]	Activation of hepatic stellate cells by interacting with the LILRB2 receptor to induce ERK signaling and increase the expression of genes that promote liver fibrosis[121]	
		Mediator of liver clock food entrainment[122]	Activation of PirB receptor→transient activation of *Per1* (ref.[122])	
		Diabetes-associated cognitive dysfunction[123]	Activation of PirB receptor→synaptic loss↓ and proinflammatory cytokine expression in microglia↑[123]	
LEAP2[e]	Hepatocytes and enterocytes	Palatable food intake↓[124]	Dopaminergic reward signalling, including in the laterodorsal tegmental area[124]	↑Steatosis[125]
		Hepatic fat accumulation under high-fat diet↓[126]	Direct inhibition of peripheral and central GHSR[57,126,127]	
		Ghrelin-induced GH secretion↓[126]		
		Body weight gain under high-fat diet↓[126]		

Table 1 | Proposed mechanisms by which some of the known hormones and hepatokines signal along the gut-liver-brain axis to impact on behaviour and physiology.

A version of this Table without references is available in the main text as Table 1.

The described effects and mechanisms are strictly based on the endogenous release and physiological mechanisms of the selected hormones and hepatokines, not pharmacology. As an example, GLP1-based drugs act directly on the bran to suppress appetite when injected peripherally, but endogenous release of GLP1 from L cells likely acts via a vagal pathway.

αMSH, α-melanocyte stimulating hormone; AgRP, agouti-related protein; ANGPTL8, angiopoietin-like protein 8; AP, area postrema; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; GFRAL, glial cell-derived neurotrophic factor heterodimeric receptor-α-like; GH, growth hormone; GHSR, growth hormone secretagogue receptor; GIP, gastric inhibitory peptide; GLP, glucagon-like peptide; HPA, hypothalamic–pituitary–adrenal axis; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; NF-κB, nuclear factor-κB; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; PAMP, pathogen-associated molecular pattern; PVN, paraventricular nucleus of the hypothalamus; PYY, peptide YY; TLR4, Toll-like receptor 4.

[a]GLP2 is always co-expressed in equimolar amounts with GLP1 but has an entirely different amino acid sequence and a separate receptor.

[b]Oxyntomodulin contains GLP1 and glucagon in its peptide sequence and, as such, signals through GLP1 and glucagon receptors, albeit with lower affinity. There, there will be significant overlap in the effects of these hormones when given at supraphysiological doses.

[c]Different isoforms of ghrelin (acylated vs desacylated ghrelin) appear to have opposite effects on certain metabolic parameters, for example, lipogenesis and lipid accumulation.[44,50]

[d]The effects of endogenous FGF21 on energy metabolism are heavily dependent on the metabolic state of the animal (for example, fasted or fed, obesity, starvation).

[e]The effects of LEAP2 depend on age, sex, duration and type of diet, ambient temperature, and intervention (for example, bariatric surgery).[128,129]

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