

# Bariatric Surgery and Gut-Brain-Axis Driven Alterations in Cognition and Inflammation

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**Abstract:** Obesity is associated with systemic inflammation, comorbidities like diabetes, cardiovascular disease and several cancers, cognitive decline and structural and functional brain changes. To treat, or potentially prevent these related comorbidities, individuals with obesity must achieve long-term sustainable weight loss. Often life style interventions, such as dieting and increased physical activity are not successful in achieving long-term weight loss. Meanwhile bariatric surgery has emerged as a safe and effective procedure to treat obesity. Bariatric surgery causes changes in physiological processes, but it is still not fully understood which exact mechanisms are involved. The successful weight loss after bariatric surgery might depend on changes in various energy regulating hormones, such as ghrelin, glucagon-like peptide-1 and peptide YY. Moreover, changes in microbiota composition and white adipose tissue functionality might play a role. Here, we review the effect of obesity on neuroendocrine effects, microbiota composition and adipose tissue and how these may affect inflammation, brain structure and cognition. Finally, we will discuss how these obesity-related changes may improve after bariatric surgery.

**Keywords:** obesity, cognitive impairment, inflammation, gut hormones, adipose tissue, bariatric surgery

## Introduction

Obesity is a major risk factor for the development of several comorbidities, including type 2 diabetes (T2DM), cardiovascular disease and several cancers.<sup>1</sup> Thirty-nine percent of the adults are overweight (25–29.9 kg/m<sup>2</sup>) and 13% are obese (BMI ≥ 30 kg/m<sup>2</sup>).<sup>2</sup> Recently, it has been found that obesity may also affect brain function and structure, as it is associated with impaired cognition and alterations in gray matter (GM) and white matter (WM).<sup>3</sup> Obesity is negatively associated with GM integrity in many brain regions such as thalamus, caudate nucleus, putamen, globus pallidus, hippocampus and nucleus accumbens.<sup>4</sup> Moreover, a higher BMI and waist-to-hip ratio (WHR) are associated with lower fractional anisotropy (FA) values, indicating a global distortion of WM integrity in multiple WM tracts, including the corpus callosum, periventricular WM and the brainstem.<sup>5,6</sup> Moreover, it is proposed that obesity increases the risk of developing dementia later in life by 60–90%, versus healthy weight individuals.<sup>7</sup> The underlying mechanisms responsible for these obesity-related brain changes are still poorly understood. However, adipose dysfunction, increased inflammation and mood disorders are suggested to play a role.<sup>8–10</sup>

Increasing evidence shows that obesity driven cognitive impairment may be reversible by weight loss,<sup>11</sup> with the largest improvements in working memory<sup>12</sup> and executive function.<sup>13,14</sup> However, substantial long-term weight loss is often hard to achieve with dietary interventions.<sup>15</sup> Though, bariatric surgery (BS) can provide a good solution. BS is an effective treatment for obesity leading to rapid and sustainable weight loss. Common procedures are the vertical sleeve gastrectomy and the Roux-en-Y gastric bypass,<sup>16</sup> which are restrictive and malabsorptive surgical procedures that induce approximately 25% total body weight loss.<sup>17</sup> Moreover, BS leads to the remission of several comorbidities, improving

glycaemic and lipid metabolism and reducing all-cause mortality.<sup>16,18–22</sup> Still little is known about the physiological changes that occur after BS. However, it is thought that hormonal alterations in the gastrointestinal tract, pancreas and adipose tissue are partially responsible for the effectiveness of BS.<sup>23</sup>

The gut-brain axis consists of a bidirectional communication system, connected through the vagus nerve, spinal fibers and sympathetic and parasympathetic fibers which are directly innervating the gastrointestinal tract.<sup>24</sup> These elements communicate through endocrine messengers, neuroimmune mediators and neuroactive metabolites. This review will focus on the gut-brain axis in obesity. In particular, we will focus on the neuroendocrine effects of ghrelin, insulin, glucagon-like-peptide-1 (GLP-1) and Peptide YY (PYY), the microbiota and its metabolites, and finally we will focus on adipokine secretion by adipose tissue on inflammation, cognition and brain structure before, and after BS. We searched the PubMed database for original articles published in English from 1996 to 2023, using appropriate search terms related to obesity (eg “obesity”, “body mass index”, “BMI”, “adiposity”, “white adipose tissue”), cognition (eg “cognition”, “memory”, “learning”), inflammation (eg “inflammation”, “neuroinflammation”, “microglia”, “immune system”), hormones (eg “gut hormones”, “GLP-1”, “insulin”, “insulin resistance”, “diabetes”, “adipokines”, “ghrelin”, “microbiome”, “microbiota”, “short chain fatty acids”, “SCFA”) and bariatric surgery (eg “bariatric surgery”, “gastric sleeve”, “gastric bypass”). Both human and animal studies investigating the mechanisms of action were included. Relevant reviews and references lists of selected articles were also examined for suitable articles. Our selection criteria for human participants were: (1) medically considered obese with a BMI  $\geq 30$  kg/m<sup>2</sup>, (2) measurement or associations between adiposity and cognition/inflammation were established and/or the effect of BS was determined, (3) control group of non-obese participants or using placebo for intervention studies. Human studies were excluded when eating disorders were documented (Table 1). Inclusion criteria for animal models were (1) induced obesity, either through diet (eg high fat diet, western diet, etc) or genetic manipulation (eg ob/ob model), (2) measurement of cognition or inflammation was established and/or the effect of BS was determined, (3) control group present (Table 2).

## The Role of Hormones

### Ghrelin

Ghrelin is an amino-acid hormone that increases appetite due to its action on the type 1a growth hormone secretagogue receptor (GHSR1a) in the hippocampus, hypothalamus and pituitary gland.<sup>94–97</sup> Ghrelin is produced mainly in the stomach, and affects the brain directly via the vagus nerve to inhibit food intake.<sup>98</sup> Obese mice show a decreased response to ghrelin,<sup>81</sup> which can be caused by lower ghrelin levels passing the blood–brain barrier (BBB)<sup>99</sup> and/or a decreased ghrelin receptor expression in the brain.<sup>70,83</sup> After consumption of a high-fat diet (HFD) in mice, the peripheral and central effect of ghrelin on food intake is reduced, indicating that ghrelin’s satiety effect is negated when following a HFD.<sup>70,83,100,101</sup> In humans, obesity is associated with decreased secretion and lower circulating levels of ghrelin.<sup>95</sup> Moreover, ghrelin levels do not increase after food intake in persons with obesity, while they do in healthy individuals.<sup>102</sup> Thus, reduced ghrelin levels are involved in increased food intake and could thereby contribute to the development of obesity.

Ghrelin can improve memory, learning and behaviour by activating the GHSR1a receptor, which is highly expressed in the hippocampus.<sup>103</sup> In C57BL/6J mice harboring thyl-green fluorescent protein, ghrelin was shown to modulate synaptic plasticity by increasing the dendritic spine density and promoting the expression of BDNF-mRNA species.<sup>104</sup> Furthermore, a ghrelin receptor antagonist (GRA) restored passive avoidance behaviours in male rats and improved spatial learning and increased activity in mice.<sup>105</sup> While animal studies tend to show a positive effect of ghrelin on cognition, one human study revealed the opposite effect. Here, it was demonstrated that increased serum ghrelin is associated with reduced performance on several cognitive domains.<sup>106</sup> Although, in humans very little research has been conducted to examine the effect of ghrelin on cognitive or behavioural functions and therefore more research should be performed. For now, it is suggested that reduced ghrelin levels might be involved in obesity-related cognitive impairment.

Ghrelin also has anti-inflammatory effects. HFD-induced inflammation in lean C57BL/6J mice was characterized by increased expression levels of toll-like receptor 4 (TLR4) in goblet cells of the intestine and interleukin-6 (IL-6), tumor

**Table 1** Summary of Included Human Studies Based on Our Inclusion Criteria

Reference	Mean BMI kg/m <sup>2</sup> ± SD	Measurement	Mean BMI Control Group, kg/m <sup>2</sup>
Alvarez Bartolomé M. et al, 2002 <sup>25</sup>	50.7 ± 9.6	The effect of PYY secretion in patients with obesity before and after VBG	Non-obese subjects
De Michele M. et al, 2002 <sup>26</sup>	33.8 ± 0.3	Association between obesity and inflammatory processes leading to carotid artery wall thickening in women	23.0 ± 0.1
Batterham RL. et al, 2003 <sup>27</sup>	33.0 ± 0.9	The effect of PYY infusion on appetite and food intake in subjects with obesity	20.5 ± 0.10
Frühbeck G. et al, 2004 <sup>28</sup>	47.1 ± 2.2	Effect of bariatric surgery on plasma ghrelin levels	NA
Stoeckli R. et al, 2004 <sup>29</sup>	AGB: 41.7 ± 1.0, LRYGB: 43.6 ± 2.0	Changes in plasma Ghrelin levels after ASGB and LRYGB	41.1 ± 1.0 (Subjects with obesity that do not undergo bariatric surgery)
Garcia-Unzueta MT et al, 2005 <sup>30</sup>	48 ± 7.0	Effect of BPD on fasting plasma ghrelin levels	NA
Batterham RL. et al, 2006 <sup>31</sup>	37.7 ± 2.4	To determine the effect of PYY on satiety	23.0 ± 0.8
Garcia-Fuentes E. et al, 2008 <sup>30</sup>	LRYGB: 53.0 ± 9.1, BPD: 54.0 ± 5.9	Effect of LRYGB and BPD on serum PYY and Ghrelin levels	26.8 ± 3.8
Karamanakos SN. et al, 2008 <sup>32</sup>	LRYGB: 46.6 ± 3.7, LGS: 45.1 ± 3.6	Changes in Ghrelin and PYY levels after LSG and LRYGB.	NA
Zhang H. et al, 2009 <sup>33</sup>	48.3 ± 7.7	The effect of LRYGB on human gut microbiota	Normal weight: 22.7 ± 2.3, post-LRYGB: 40.6 ± 5.4
Rigamonti AE. et al, 2011 <sup>34</sup>	47.3 ± 3.3	The effect of cholestyramine or placebo on postprandial PYY response in obese women	NA
Salehi M. et al, 2011 <sup>35</sup>	Before LRYGB: 52.0 ± 2.0, After LRYGB: 33.0 ± 1.0	The effect of bariatric surgery on insulin secretion	33.0 ± 2.0
Dar MS. et al, 2012 <sup>36</sup>	44.8 ± 1.1	The postprandial GLP-I response after LRYGB	Lean participants 22.9 ± 0.9, 10 year post-LRYGB: 40.4 ± 10.2
Peterli R. et al, 2012 <sup>37</sup>	LRYGB: 47.6 ± 6.8, LSG: 44.7 ± 5.3	Hormonal changes after LRYGB and LSG	NA
Ramón JM. et al, 2012 <sup>38</sup>	LRYGB: 44.0 ± 2.0, LGS: 43.5 ± 3.0	Effect of LRYGB vs LSG on Glucose and Gut Hormones	NA
Tschoner A. et al, 2012 <sup>39</sup>	42.42 ± 3.98	The association between inflammatory markers and fat depots in obesity and after bariatric surgery	NA

(Continued)

Table I (Continued).

Reference	Mean BMI kg/m <sup>2</sup> ± SD	Measurement	Mean BMI Control Group, kg/m <sup>2</sup>
Barazzoni R. et al, 2013 <sup>40</sup>	Mod-obese: 31.0 ± 1.8, Severe obese: 45.4 ± 0.9	Effect of LRYGB on plasma ghrelin levels.	23.1 ± 1.0
Salinari S. et al, 2013 <sup>41</sup>	43.1 ± 5.3	Effect of insulin clearance after LRYGB	24.6 ± 1.3
Tsoli M. et al, 2013 <sup>42</sup>	BPD: 57.6 ± 9.9, LSG: 43.7 ± 2.1	Changes in GLP-I and PYY after LSG and BPD	NA
Verdam FJ. et al, 2013 <sup>43</sup>	44.2 ± 2.3	Association between intestinal microbiota composition and systemic inflammation in obesity	28.2 ± 3.3
Cahill F. et al, 2014 <sup>44</sup>	Whole cohort: 26.68 ± 4.9	The correlation between fasting serum total PYY and obesity/adiposity	NA
Yousseiff A. et al, 2014 <sup>45</sup>	451.5 kg/m <sup>2</sup>	Effect of LRYGB and LSG on PYY and GLP-I	NA
Cheke LG. et al, 2017 <sup>46</sup>	High IR: 31.85 ± 7.0	The impact of insulin resistance on cognitive function	Low IR: 23.73 ± 7.3
Bove RM. et al, 2016 <sup>47</sup>	37.3 ± 3.0	Association between adiposity and cognitive function in obese men	NA
Kruljac I. et al, 2016 <sup>48</sup>	LSG: 46.8 (range 44.9–50.9), LRYGB: 41.4 (range 39.8–42.8)	Changes in metabolic hormones after bariatric surgery	NA
Palleja A. et al, 2016 <sup>49</sup>	Not specified, inclusion criteria BMI>35	The effect of LRYGB on gut microbiota.	NA
Barczynska R. et al, 2018 <sup>50</sup>	Range: 31.71–41.18	Differences between bacterial microbiota and fatty acids in faeces of obese children	Range: 18.25–22.38
Krumbeck JA. et al, 2018 <sup>51</sup>	Median (IQR) 36.7 (8.5)	The effect of Bifidobacterium endotoxemia in subjects with obesity	Placebo supplement (BMI not shown)
Dao MC. et al, 2019 <sup>52</sup>	44.1 ± 6.2	The effect of bariatric surgery on Akkermansia muciniphila abundance	NA
Depommier C. et al, 2019 <sup>53</sup>	39.81 ± 4.77 (Akkermansia muciniphila supplementation)	The effect of Akkermansia muciniphila supplementation on inflammation in subjects with obesity	37.63 ± 5.82 (placebo supplement)
Guida C. et al, 2019 <sup>54</sup>	47 ± 8.4	Change in PYY concentrations after bariatric surgery and compared to healthy controls	22.24 ± 2.1
Huang T. et al, 2019 <sup>55</sup>	16% of total cohort was obese (BMI>30kg/m <sup>2</sup> )	Association between adiposity and cognitive performance in human.	NA
Hui SCN. et al, 2019 <sup>56</sup>	35.2 (range 32.5–38.6)	Change in adipose tissue after bariatric surgery	NA

<b>Maïmoun L. et al, 2019<sup>57</sup></b>	41.9 ± 4.5	Change in body composition after bariatric surgery	NA
<b>Marseglia A. et al, 2019<sup>58</sup></b>	Cohort study, 14.2% obese in pre-diabetes group, 27.7% obese in diabetes group (BMI ≥ 30 kg/m <sup>2</sup> )	The relation between diabetes (insulin resistance) and cognitive function	40.6% normal weight in pre-diabetes group, 28.1% normal weight in diabetes group.
<b>Perakakis N. et al, 2019<sup>59</sup></b>	LSG: 49.8 ± 8.2, LRYGB: 50.2 ± 9.1	The effect of bariatric surgery on circulating levels of gastrointestinal hormones	NA
<b>Svane MS. et al, 2019<sup>60</sup></b>	LSG: 33.4 ± 2.4, LRYGB: 33.5 ± 2.1	Hormone secretion after bariatric surgery	Unoperated control group 33.4 ± 1.7
<b>Tsouristakis AI. et al, 2019<sup>61</sup></b>	AGB: 41.8 ± 0.9, LRYGB: 47.2 ± 0.7	Effect of bariatric surgery on appetitive hormones	NA
<b>Lopez-Nava G. et al, 2020<sup>62</sup></b>	ESG: 38.3 ± 1.8, LSG: 39.2 ± 1.5	The effect of bariatric surgery on gut and metabolic hormones	NA
<b>Han K. et al, 2021<sup>63</sup></b>	40.29 ± 8.06	The effect of PYY on inflammation, CD4+ cells and immune activation	24.17 ± 2.17
<b>Kanazawa A. et al, 2021<sup>64</sup></b>	29.5 ± 4.4 (symbiotic treatment)	The effect of symbiotic supplementation on inflammation in patients with obesity	29.1 ± 4.4 (placebo treatment)
<b>Leyrolle Q. et al, 2021<sup>65</sup></b>	41.1 ± 8.9 (used Inulin supplements)	The effect of prebiotic administration on cognition in patients with obesity	36.5 ± 6.1 (used placebo)
<b>Martínez-Cuesta MC. et al, 2021<sup>66</sup></b>	>30.0	Taxonomic characterization and short-chain fatty acids production of the obese microbiota	18.0–25.0
<b>Agarwal K. et al, 2022<sup>67</sup></b>	LSG: 42.5 ± 1.7, LRYGB: 46.4 ± 1.8	The effect of weight loss on postprandial gut hormone responses	MWL: 38.8 ± 2.6
<b>Lejawa M. et al, 2022<sup>68</sup></b>	MHO: 31.38 (range 30.63–33.05), MUO: 34.02 (range 33.03–37.02)	Effect of obesity on inflammation	23.36 (range 21.78–24.10)
<b>Vreeken D. et al, 2023<sup>11</sup></b>	42.1 (range 36.7–44.0)	Effect of bariatric surgery on inflammation and cognition	NA

**Abbreviations:** LRYGB, Laparoscopic Roux-en-Y gastric bypass; LSG, Laparoscopic sleeve gastrectomy; BPD, Biliopancreatic diversion; ASGB, adjustable gastric banding; GLP-1, glucagon-like peptide 1; PYY, peptide YY; IR, insulin resistance; VBG, vertical-banded gastroplasty; ESG, endoscopic sleeve gastroplasty; MWL, medical weight loss; IQR, inter quartile range; MHO, metabolic healthy obesity; MUO, metabolic unhealthy obesity; NA, not applicable.

**Table 2** Summary of Included Animal Studies Based on Our Inclusion Criteria

Reference	Animals	Measurement	Control Group
Turnbaugh PJ. et al, 2006 <sup>69</sup>	Obese (ob/ob) mice	The energy harvesting capacity of the obese microbiota	Lean (+/+) mice
Briggs DI. et al, 2010 <sup>70</sup>	Male C57Bl6 mice on HFD	The effect of diet induced obesity on ghrelin resistance and cognition.	Male C57Bl6 mice on chow diet
Porter DW. et al, 2010 <sup>71</sup>	Swiss TO mice on HFD	The effect of GLP-I receptor agonist on cognitive function in obese mice	Swiss TO mice on standard rodent maintenance diet
Pratchayasakul W. et al, 2011 <sup>72</sup>	Male Wistar rats on HFD	Effect of insulin on long-term depression	Male Wistar rats on chow diet
Lam YY. et al, 2012 <sup>73</sup>	Female C57BL/6J mice on HFD	Microbiota change in diet-induced obese mice	Female C57BL/6J mice on control diet
Lee YS. et al, 2012 <sup>74</sup>	Diabetic male ob/ob mice injected with rAd-GLP-I	The effect of GLP-I receptor agonist on macrophage infiltration inflammation	Pair-fed and rAd-βgal-treated pair-fed control mice
Kappe C. et al, 2012 <sup>75</sup>	Male obese (ob/ob) mice	The neuroprotective and anti-inflammatory properties of GLP-I in the brain of obese mice	Male lean (+/+) mice
Everard A. et al, 2013 <sup>76</sup>	Male C57BL/6 on HFD diet, and chow diet administered with Akkermansia muciniphila	The effect of Akkermansia muciniphila administration on inflammation in obese mice	Glycerol administered male C57BL/6 mice
Liou AP. et al, 2013 <sup>77</sup>	C57BL/6J DIO mice on HFD	The effect of gastric bypass on gut microbiota shifts, weight and adiposity	Male, age-matched, germ-free Swiss Webster mice
Porter WD. et al, 2013 <sup>78</sup>	Male ob/ob mice with subcutaneous Liraglutide injections	The effect of GLP-I receptor agonist on memory in obese mice	Male ob/ob mice with saline vehicle
Lennox R. et al, 2014 <sup>79</sup>	Male NIH Swiss mice on HFD	The effect of metformin and GLP-I receptor agonist on cognitive function in obese mice	Lean control mice
Pintana H. et al, 2014 <sup>80</sup>	Adult male Wistar rats on HFD	The difference between cognitive function and mitochondrial dysfunction in obese insulin resistant and control rats.	Adult male Wistar rats on chow diet
Uchida A. et al, 2014 <sup>81</sup>	Male C57BL/6 mice on HFD	The effect of diet induced obesity and bariatric surgery on ghrelin secretion and inflammation	Male C57BL/6 mice on chow diet
Hamilton MK. et al, 2015 <sup>82</sup>	Male Wistar rats on HFD	Changes in gut microbiota in HFD fed rats	Male Wistar rats on chow diet
Naznin F. et al, 2015 <sup>83</sup>	Male C57BL/6J mice on HFD	The effect of diet induced obesity on ghrelin resistance and inflammation	Male C57Bl6 mice on chow diet
Waise TMZ. et al, 2015 <sup>84</sup>	Male C57BL/6J mice on HFD	Effect of obesity on inflammatory markers	Male C57BL/6J mice on chow diet

<b>Yan M. et al, 2016<sup>85</sup></b>	GK rats	The effect of bariatric surgery on intestinal Akkermansia muciniphila in obese rats.	Wistar rats
<b>Arnoldussen IAC. et al, 2017<sup>8</sup></b>	Male LDLr <sup>-/-</sup> leiden mice on HFD	The effect of butyrate on cognition in obese mice	Male LDLr <sup>-/-</sup> leiden mice on chow diet
<b>Sa-NGuanmoo P. et al, 2017<sup>86</sup></b>	Male Wistar rats on HFD	Cognitive function in obese induced insulin resistance	Male Wistar rats on chow diet
<b>Pétrault O. et al, 2019<sup>87</sup></b>	C57BL/6J mice on HFD	Effect of visceral adiposity on cognitive function in obese mice	C57BL/6J mice on chow diet
<b>Zhang P. et al, 2019<sup>88</sup></b>	Male C57BL/6J mice on high palmitic acid diet	Effect of microbiota on cognitive function in obese mice	Male C57BL/6J mice on low fat diet
<b>Liu L. et al, 2020<sup>89</sup></b>	Male Sprague-Dawley rats on HFD	The effect of white adipose tissue browning after LSG in obese rats	NA
<b>Liu Z. et al, 2020<sup>90</sup></b>	Female C57BL/6J mice on HFD	The effect of diet on cognitive function and depression	Female C57BL/6J mice on chow diet
<b>Liu Z. et al, 2020<sup>91</sup></b>	Male obese homozygous Lepr (db/db) mice	Change in SCFA after intermittent fasting and its effect on cognitive function in diabetic obese mice	Heterozygous Lepr (db/m) mice
<b>Shi H. et al, 2020<sup>92</sup></b>	Male C57BL/6J mice on high fat and high fiber diet	The effect of microbiota-accessible carbohydrates on neuroinflammation and cognition in obese mice	Male C57BL/6J mice on chow diet
<b>Doncheva AI. et al, 2022<sup>93</sup></b>	Male C57BL/6J Srgn <sup>+/+</sup> mice on high fat and high sucrose diet, C57BL/6N mice on 60% fat diet.	The effect of Serglycin on adipose tissue inflammation in obesity	Male C57BL/6J Srgn <sup>+/+</sup> mice on chow diet, C57BL/6N mice 10% fat diet.

**Abbreviations:** HFD, high fat diet; Lepr, leptin receptor deficiency; GLP-I, glucagon-like peptide I; PYY, peptide YY; DIO, diet-induced obesity; SCFA, short chain fatty acids; LDR, low-density lipoprotein; Srgn, serglycin; NA, not applicable

necrosis factor alpha (TNF- $\alpha$ ), ionized calcium-binding adaptor molecule 1 (IBA1) and eosinophil surface receptor 1 (EMR-1) in the nodose ganglion and hypothalamus.<sup>84</sup> Ghrelin administration reduced cytokine expression and thereby ameliorated HFD-induced inflammation.<sup>84</sup> This anti-inflammatory effect of ghrelin also blocks the NF- $\kappa$ B pathway and reduces IL-6, IL-1 $\beta$  and TNF- $\alpha$  expression in endothelial cells.<sup>107</sup> An in vitro model showed decreased levels of leptin induced inflammatory cytokines after ghrelin treatment, suggesting that ghrelin can control immune cell activation and inflammation.<sup>108</sup> Finally, there seems to be a relation between ghrelin resistance and metabolic inflammation, which both are related to obesity and can be improved by calorie restriction.<sup>109</sup>

Ghrelin affects meal initiation and as a consequence increases calorie intake,<sup>110</sup> which might be circumvented through bariatric surgeries. The vertical sleeve gastrectomy involves the removal of the gastric fundus, the primary source of ghrelin, leading to a reduction of fasting and postprandial ghrelin on short and long term.<sup>32,38,45</sup> In comparison, the effect of biliopancreatic diversion on ghrelin is much lower as the gastric fundus is maintained which induces no change<sup>30,42</sup> or increased ghrelin levels.<sup>28,111</sup> Results on Roux-en-Y gastric bypass remain inconclusive, as some studies reveal decreased ghrelin levels, even 5 years post-surgery,<sup>28,29,37</sup> while others showed either no change<sup>32,48</sup> or higher post-operative ghrelin levels.<sup>40,61</sup> Increased ghrelin levels may arise from a compensatory mechanism after weight loss, whereas the difference in ghrelin levels after surgery may be explained by different surgeons performing the surgeries. The remaining gastric pouch and alimentary limb can differ in size and length as these are determined by the surgeon, causing differences in ghrelin levels. In conclusion, altered ghrelin levels in obesity might be involved in the development of obesity-related cognitive impairment and inflammation, but its levels seem to be restored after BS.

## Insulin

Insulin is secreted by  $\beta$ -cells in the islet of Langerhans in the pancreas and regulates glucose homeostasis, via its hypoglycaemic effect.<sup>112</sup> Insulin is initially released after food intake through the readily releasable pool within the plasma membrane of pancreatic B-cells, while the second release is more sustained and derives from granules stored in the reserve pool which resides deeper within the cell.<sup>113</sup> Insulin can peripherally activate glucose transporter type 4 (GLUT4), which subsequently transports glucose to the liver, muscles and adipose tissue.<sup>114</sup> Individuals with obesity have increased levels of insulin and therefore have an increased risk of insulin resistance, compared to lean controls.<sup>68</sup> Insulin resistance is described as the failure of tissues to respond to the constant release of insulin, increasing insulin levels independent of blood glucose, a phenomenon known as hyperinsulinemia.<sup>115</sup> Obesity is also a known risk factor for the development of T2DM as it is associated with abnormal fasting glucose levels and impaired glucose tolerance.<sup>116</sup>

Disrupted glycaemic control not only affects peripheral organs but also the brain, determined by impaired brain insulin sensitivity.<sup>72,86</sup> Moreover, deficits in memory,<sup>46</sup> attention and learning<sup>117</sup> have been implicated in T2DM. Disrupted glycaemic control is associated with high glucose levels, which induce vasoconstriction and therewith also reduce the blood flow to the brain,<sup>118</sup> which may explain the decreased GM and WM volumes observed in diabetes type I and II.<sup>119,120</sup> Nonetheless, insulin driven cognitive impairment already arises in pre-diabetes, as pre-diabetic individuals perform poorer on memory and cognitive tasks, show a smaller total brain volume and have reduced WM integrity compared to non-diabetic participants.<sup>58,121,122</sup> These memory impairments in pre-diabetics are directly attributed to insulin resistance and not to increased glucose levels,<sup>123</sup> suggesting that obesity-related insulin resistance might induce changes in cognition and the brain.

Insulin resistance is associated with increased production of reactive oxygen species (ROS), leading to swelling and conformational changes in the mitochondria.<sup>80,86</sup> ROS can trigger mitochondrial membrane permeability and consequently mitochondrial dysfunction. Proteins from the mitochondrial intermembrane space are expelled and cause apoptosis via various pathways.<sup>124</sup> Oxidative stress driven by ROS notably affects the brain as it impairs regeneration and limits the degree of antioxidant products.<sup>125</sup> Finally, ROS is a modulator of NF- $\kappa$ B and mitogen-activated protein kinase pathways,<sup>126</sup> and can thereby activate the brain's resident immune cells, the microglia, and increase levels of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$ .<sup>125</sup> All these changes alter adenosine triphosphate (ATP) production, which is highly important to maintain neuronal functions.<sup>127</sup> In addition, activation of these pathways induces apoptosis and creates a domino effect; ATP is released extracellularly by injured and apoptotic cells,<sup>128</sup> which in turn activates microglia and the release of cyclooxygenase-2, TNF- $\alpha$  and IL6, ultimately leading to more neuronal death.<sup>129</sup>



Roux-en-Y gastric bypass restores fasting insulin levels and improves insulin sensitivity.<sup>130</sup> Increased secretion of GLP-1 and gastric inhibitory polypeptide (GIP) are driving forces for insulin release due to their insulinotropic effects.<sup>35</sup> It is suggested that bypassing a portion of the small intestine inhibits the production and secretion of GLP-1 and GIP and might reduce insulin resistance. Moreover, it is believed that a longer bypass of the proximal intestine leads to a higher reduction of insulin resistance.<sup>131</sup> Therefore, it is assumed that the biliopancreatic diversion is more successful in terms of restoring insulin sensitivity compared to Roux-en-Y gastric bypass. This is independent from weight loss, as the difference in insulin resistance between surgeries was observed in the early post-operative stages.<sup>131</sup> Diabetic and non-diabetic patients with obesity confirmed previous results, as they showed increased insulin clearance after bypassing both the duodenum and proximal jejunum versus bypassing solely the duodenum.<sup>41</sup> In summary, obesity-induced insulin resistance is associated with (neuro)inflammation, cognitive impairment, albeit BS seems to reverse these negative effects.

## Glucagon-Like-Peptide-I

GLP-1 is an incretin hormone, which upon food ingestion, is secreted by L cells in the ileum and by neurons in the nucleus tractus solitarius. GLP-1 has an anorectic effect. It increases insulin synthesis and secretion, and inhibits glucagon, and therewith decreases blood sugar levels and slows down digestion.<sup>132</sup> In obesity, the anorectic effect of GLP-1 seems to be reduced, since ob/ob mice show a reduction of GLP-1 receptors in the cortex and hippocampus.<sup>75</sup> Additionally, clinical studies also indicated that weight gain promotes functional deficits in GLP-1 signalling, which maintain the obese phenotype.<sup>133</sup>

Previous research showed that GLP-1 can enhance associative and spatial learning via the GLP-1 receptor (GLP-1R). It was demonstrated that GLP-1R deficient mice show deficits in contextual fear conditioning which restored after hippocampal *Glp1r* gene transfer.<sup>134</sup> Additionally, in rats, intranasal administration of synthetic GLP-1 analogues increased spatial learning capacities as shown in the Morris water maze (MWM) and passive avoidance paradigm.<sup>134</sup> Long-term potentiation, a mechanism which strengthens synaptic connections and important for learning and memory<sup>135</sup> is increased in obese ob/ob mice after GLP-1 agonist administration compared to controls.<sup>78</sup> Moreover, these mice showed improved glycaemic control.<sup>78</sup> These findings were supported by HFD induced ob/ob mice which showed decreased body weight, improved performance on the object recognition test and improved non-fasting insulin levels after daily injections of Liraglutide, a GLP-1 agonist.<sup>71</sup> Memory improvements were observed in an Alzheimer mouse model after administration of insulin together with exenatide (a GLP-1 agonist), compared to insulin alone, suggesting that the neuroprotective effect of GLP-1 does not depend on insulin.<sup>136</sup> In addition, GLP-1 analogue consumption in HFD induced obese mice also increased neurogenesis and proliferation in the hippocampus, a region involved in memory consolidation and storage.<sup>79</sup> Thus, GLP-1 plays an important role in cognitive function, suggesting that functional deficits in GLP-1 might commit to obesity related cognitive impairment.

GLP-1 has anti-inflammatory effects as it inhibits the production of cytokines after lipopolysaccharides (LPS) induction.<sup>137</sup> In vitro and in vivo studies demonstrate that GLP-1 agonists activate GLP-1R, which promotes pre-adipocytes proliferation and inhibits apoptosis and therewith increase adipocyte formation and improve lipid homeostasis.<sup>138</sup> Animal studies also provided evidence for the anti-inflammatory effect of GLP-1. Recombinant adenovirus producing GLP-1 administration in obese ob/ob mice resulted in decreased expression of proinflammatory cytokines such as IL-6, TNF- $\alpha$  and monocyte chemoattractant protein-1 in adipose tissue. Moreover, LPS-induced inflammation and expression of M1 macrophage-specific genes was decreased in these GLP-1 treated ob/ob mice.<sup>74</sup> Recently, GLP-1 agonists are being prescribed as medication to lose weight in for example diabetic patients. GLP-1 agonists may exert a positive effect on glucose homeostasis, which help to maintain weight, and directly affect adipocytes.<sup>74</sup> Besides, human trials also highlighted the potential of GLP-1 agonists to significantly reduce inflammation.<sup>139</sup> These anti-inflammatory effects might also contribute to the neuroprotective effect of GLP-1. It was revealed in an animal study that the proglucagon gene and TNF- $\alpha$  expression levels were reduced in obese ob/ob mice, compared to control mice.<sup>75</sup> Moreover, a positive correlation between TNF- $\alpha$  and proglucagon mRNA expression levels was found in control and ob/ob mice. Furthermore, it was stated that activated microglia, induced by LPS, reduced the secretion of GLP-1, while TNF- $\alpha$  and proglucagon levels acutely and transiently increased. This indicates that the acute

effect of LPS treatment initially inhibits the GLP-1 secretory mechanism. It was speculated that the correlation of pro-inflammatory cytokines to mRNA expression of a neuroprotective element confers increased protection to neurons whilst fighting off pathogens.<sup>75</sup>

BS has also been shown to increase GLP-1 levels.<sup>59,60</sup> For Roux-en-Y gastric bypass, this elevation in GLP-1 levels remained 10 years after surgery.<sup>36</sup> Moreover, GLP-1 was positively correlated with weight loss post-operatively.<sup>140</sup> Sleeve gastrectomy also increased GLP-1, albeit levels were markedly lower one year after surgery compared to the Roux-en-Y gastric bypass group.<sup>37</sup> In summary, deficits in GLP-1 signalling are linked to obesity, cognitive changes and increased inflammation. Nonetheless, BS can restore GLP-1 levels and thereby improve obesity-related alterations.

## Peptide YY

Peptide YY<sub>1-36</sub> (PYY) is secreted postprandially from L cells in ileum and colon. It is an anorexigenic hormone and is converted to PYY<sub>3-36</sub> in the circulation when cleaved by dipeptidyl-peptidase IV (DPP-IV). Circulating levels of PYY<sub>3-36</sub> are more abundant than PYY<sub>1-36</sub>. PYY<sub>3-36</sub> has a high affinity for the Y2 receptor, and this inhibitory G-coupled receptor decreases levels of cyclic-AMP and intracellular calcium.<sup>141</sup> It is thought that the anorexigenic effect of PYY<sub>3-36</sub> is induced by Y2 receptor stimulation in the hypothalamus, which then increases neuropeptide Y effects and consequently reduces hunger by increasing satiety.<sup>44</sup> The ileum and colon have the highest levels of PYY<sub>1-36</sub>. In subjects with normal weight or obesity, plasma concentrations of PYY were significantly increased after a high-fat meal, suggesting that PYY secretion is primarily determined by the fat content of the meal.<sup>34</sup> In obesity, the secretory profile of PYY has been altered. Fasting PYY levels are negatively correlating with BMI and are diminished in participants with obesity.<sup>25,27,54</sup> Individuals with obesity showed not only decreased levels of circulating PYY but also lower postprandial secretion of PYY in comparison to healthy individuals.<sup>31</sup> Nonetheless, results are contradictory as a large population-based study (2094 participants – 75%female) showed no differences in PYY levels between participants with obesity, overweight and a healthy weight.<sup>44</sup> PYY gene expression and subsequent PYY secretion are increased by the histone deacetylase inhibitory activity of short-chain fatty acids (SCFA; eg butyrate and propionate). SCFA is a product of carbohydrate fermentation by the gut microbiota and is thus linked to fiber intake. Therefore, previous results might not depend on obesity per se but relay more the current diet of participants.<sup>142</sup> Moreover, it is known that the microbiota composition in obesity is significantly altered compared to lean individuals, which can also impair SCFA expression levels.<sup>143</sup> Accordingly, it is suggested that altered SCFA expression levels, as a consequence of lower diet quality and a dysbalanced microbiota, could contribute to differences in PYY levels in obesity and normal weight.

The Y2 receptor is widely expressed, making it possible for PYY to activate neural circuits throughout the brain. Notably, the mesolimbic, nigrostriatal dopaminergic pathways, brainstem and orbitofrontal cortex were activated after peripheral injection of PYY<sub>3-36</sub> in healthy participants. Moreover, it was shown that PYY could switch activity in areas predicting calorie intake from a homeostatic (eg hypothalamus) to a more hedonic area (eg orbitofrontal cortex).<sup>144</sup> Subjects showed similar BOLD patterns after feeding and after PYY<sub>3-36</sub> infusions during the fasted state in brain reward regions such as insula, left nucleus accumbens and left orbitofrontal cortex.<sup>145</sup> This widespread activation was also seen in Long Evans rats.<sup>146</sup> After peripheral PYY administration, brain activity was detected in the nucleus tractus solitarius, hypothalamic arcuate nucleus, paraventricular nucleus but also in hedonic centres such as the amygdala and the nucleus accumbens.<sup>146</sup> PYY also increased novelty seeking behaviours in a dose-dependent manner, determined by the novel object exploration test,<sup>147</sup> in animals administered with PYY compared to controls. On the contrary, it has been found that PYY can impair selective associative learning, spatial working memory and goal-directed behaviour in mice, determined by the latent inhibition paradigm and water maze test.<sup>148</sup> Another study revealed that increased PYY levels were associated with decreased nesting behaviour and increased food intake, which could be restored by a T2 receptor antagonist.<sup>149</sup>

PYY is also strongly involved in the immune system, yet its role in inflammation is still uncertain. The PYY promoter gene contains two potential NF-κB binding domains. In vitro stimulation of the NF-κB pathway by TLR agonists lead to an 80 to 100% increased expression of PYY. This was seen after activation of TLR 2 and 6, which have a strong effect on NF-κB.<sup>150</sup> Although, TLR 7 and 8 agonists did not elicit an increase in NF-κB activation they still increased PYY expression. PYY derived from PYY<sub>3-36</sub>, inhibits gut motility by decreasing neuronal activity, while PYY<sub>1-36</sub> enhances gut

motility by increasing muscle contractions.<sup>150</sup> Therefore, increased PYY induced by TLR activity might increase colonic motility, a physical mechanism to eliminate pathogens and restrict nutrient availability in the infected area. Additionally, colitis is negatively associated with PYY plasma levels and deregulated intestinal motility. Moreover, PYY increases the production and degranulation of invariant natural killer T cells, is associated with increased CD4+ T cell activation, and it increases immune activity.<sup>63</sup> These results suggest that PYY levels increase as a host response to colonic infection.

Both sleeve gastrectomy and gastric bypass have been shown to increase PYY levels 6 month post-surgery.<sup>54</sup> PYY fasting levels were significantly higher after sleeve gastrectomy, whereas such effect was not seen after Roux-en-Y gastric bypass. Both the sleeve gastrectomy and Roux-en-Y gastric bypass improved postprandial levels of PYY.<sup>62,67</sup> However, diet-induced weight loss showed no significant changes in PYY levels. Therefore, these improvements may be attributed to a mechanistical effect of the surgery and not the weight loss itself.<sup>67</sup>

## Microbiota and Short Chain Fatty Acids

The gastrointestinal tract is home to a multitude of bacteria, and dysbiosis in the gut microbiota has been associated with obesity.<sup>73,88</sup> Notably, HFD induced obese mice showed decreased microbiota diversity, determined by increased Firmicutes and Oscillibacter abundance, decreased levels of *Bacteroidetes* and *Lactobacillus* and increased *Firmicutes/Bacteroidetes* ratio.<sup>73,82,151</sup> Similarly in humans, obesity is accompanied by reduced bacterial diversity, increased abundance of potential proinflammatory proteobacteria and decreased *Bacteroidetes/Firmicutes* ratio.<sup>43</sup> Other important features for microbiota diversity are the SCFA, which are the primary metabolites produced in the colon after fermentation of fibers and non-digestible starch by the gut bacteria.<sup>152</sup> In particular, acetate and propionate are produced by *Bacteroidetes*, while butyrate is produced by *Firmicutes*.<sup>152</sup> Previous research shows contradictory results, including positive and negative relationships between SCFA and obesity.<sup>153</sup> Martínez-Cuesta et al compared the metabolite production of the microbiota from obese and normal weight participants cultured in high and normal energy medium.<sup>66</sup> Here, it was found that the microbiota of obese participants cultured in high energy medium produced more SCFA compared to microbiota from normal weight participants cultured in both mediums. This finding suggests that energy harvesting is optimized in the microbiota of participants with obesity. Moreover, obese ob/ob mice showed an enrichment in pathways encoding polysaccharide digesting enzymes compared to lean mice, supporting the enhanced energy harvest potential of the obese microbiota.<sup>69</sup> In comparison, SCFA concentration in the stool of children with obesity, but not overweight, was lower compared to normal weight children.<sup>50</sup> Obesity is induced by a low fiber and high fat diet, potentially explaining the observed negative relation between SCFA and obesity. As results are inconsistent, more studies with a larger cohort are needed to define the direction and causality of this relationship, but also to identify other factors involved in SCFA production, excretion and absorption in humans.

Alterations in the microbiota also seem to be associated with mood, cognition and behaviour. In mice, *Bacteroidetes* were negatively associated with performance in the Y-maze and object recognition test, indicating that *Bacteroidetes* play a role in reference and working memory.<sup>88</sup> It is known that the gut microbiota can directly influence the central nervous system via the kynurenine pathway and as a consequence of tryptophan metabolism. The gut may influence emotional regulation and has been implicated in mood disorders such as anxiety via the connection between the gut and brain.<sup>154</sup> A high-fiber diet reduced anxiety in mice, reflected by increased time spent in the open arm and elevated plus-maze test.<sup>90</sup> These mice also showed significantly improved performance on the MWM task. In humans, improved mood was demonstrated after six weeks of prebiotic consumption.<sup>155</sup> Additionally, the Scale of Positive and Negative Experience revealed a decrease in negative emotions and enhanced flexibility in subjects with obesity after intake of prebiotics.<sup>65</sup> Moreover, improvements in the MWM were linked to a healthier gut microbiota profile and their metabolites, including serotonin, tauroursodeoxycholic acid (TUDCA) and 3-indolepropionic acid (IPA).<sup>91</sup> Intermittent fasting in obese diabetic mice (db/db model) was also shown to improve cognition, mitochondrial function, post-synaptic density and insulin sensitivity. Individual metabolite administration revealed that the observed improvements were induced by SCFA, TUDCA, IPA and serotonin.<sup>91</sup> Moreover, after antibiotic administration, these positive effects diminished, highlighting the impact of the gut microbiota.

As mentioned before, SCFA are the metabolic products of fiber fermentation by anaerobic bacteria in the gut. They are important fuel for intestinal epithelial cells, but also have the ability to act on different inflammatory cells, including

macrophages and neutrophils.<sup>156</sup> Butyrate, for example, is able to increase peripheral regulatory T-cells and induces secretion of GLP-1 from intestinal endocrine cells, and thereby decreases inflammation.<sup>157</sup> Butyrate can regulate inflammation in the epithelium by increased production of anti-inflammatory cytokines and activation of dendritic cells.<sup>158</sup> Butyrate administration in mice can decrease microglial inflammation after HFD-induced obesity, reflected by decreased ionized calcium-binding adapter molecule 1 expression in the thalamus and hippocampus.<sup>8</sup> Supplementation of a fiber-rich diet improved cognitive impairment, gut microbiota dysbiosis, endotoxemia and systemic inflammation.<sup>92</sup> Moreover, SCFAs might inhibit inflammation in the central nervous system as valproic acid, butyrate, and trichostatin A induced anti-neuroinflammatory and neuroprotective effects in rats with brain ischemia.<sup>156</sup> These results indicate the importance of a healthy diet, microbiota and metabolite production in order to regulate inflammatory processes.

The gut microbiota is important to protect the gut mucosal barrier and maintaining a proper barrier function via the production of butyrate<sup>159</sup> which is transported into epithelial cytoplasm and used as cellular fuel after  $\beta$ -oxidation inducing epithelial proliferation.<sup>158</sup> When this mechanism fails, the gut may become permeable and increase LPS-induced translocation of bacterial metabolites into the circulation.<sup>23</sup> Increased LPS activates TLR which further triggers the release of inflammatory cytokines, alteration of white adipose tissue and impairment of insulin sensitivity.<sup>160,161</sup> Probiotic administration has shown to reduce LPS inflammation and improve gut barrier function in vitro,<sup>162</sup> probably as a consequence of SCFA production, as they are derived from fiber fermentation.<sup>142</sup> Participants with overweight and obesity showed decreased plasma LPS, proinflammatory chemokines and white blood cells after three months pasteurised *Akkermansia muciniphila* supplementation.<sup>53</sup> However, supplementation with *Bifidobacterium adolescentis* and *Bifidobacterium lactis* did not change lipopolysaccharide-binding protein (LBP) or plasma LPS levels in participants with obesity.<sup>51</sup> Synbiotic supplementation of *Lactobacillus paracasei*, *Bifidobacterium breve* and galactooligosaccharides also did not improve inflammatory markers nor glycaemic control compared to controls.<sup>64</sup> In conclusion, the gut microbiota is involved in the maintenance of a healthy gut barrier by the regulation of inflammation, in which every bacteria has its own effect.

BS leads to anatomical changes and thereby alters the passage of nutrients and increases the pH of the digestive tract. This creates a shift from an anaerobic environment towards a more aerobic environment. Therefore, BS will also create a shift in microbial composition.<sup>23,163</sup> Every BS procedure will induce different anatomical changes in the digestive tract, and therewith alter the gut microbiota in distinct ways.<sup>164</sup> Studies have observed increased levels of *Bacteroidetes*, *Proteobacteria* and increased variety of *Fusobacteria* and the *Verrucomibia* phyla, with decreasing levels of *Firmicutes* and *Actinobacteria* in mice and men after gastric bypass.<sup>33,49,77</sup> *Akkermansia muciniphila* is of particular interest as it is inversely associated with obesity.<sup>52</sup> pH changes accompanied by Roux-en-Y gastric bypass also increase levels of *Akkermansia muciniphila*.<sup>33</sup> Moreover, *Akkermansia muciniphila* is associated with mucin degradation,<sup>165</sup> increased GLP-1 levels,<sup>85</sup> reversed adipose driven inflammation, insulin sensitivity and fat reduction,<sup>76</sup> all contributing to a healthier intestinal barrier function. Nevertheless, the changes in gut microbiota post-BS display large variability between patients, which could also contribute to differences in weight loss.<sup>166</sup> It is unclear whether the change in gut microbiota composition after BS is induced by a significant change in diet or reduction in gastric volume.<sup>167</sup> In summary, BS induces changes in the gut microbiota composition which vary between patients and surgical procedures. However, increased microbiota diversity after BS might improve adipose tissue, gut barrier integrity, insulin sensitivity and many more.

## Adipose Tissue

Adipose tissue is an endocrine organ which recently gained more attention.<sup>168</sup> Adipose depots are an intricate mesh, involving adipocytes, preadipocytes, stem cells and immune cells.<sup>169</sup> Adipocytes are most abundant in the white adipose tissue (WAT), which constitutes 95% of the humans body fat. Brown adipose tissue (BAT) constitutes 2% and beige adipose tissue constitutes roughly 3% of the humans body fat.<sup>169</sup> The main function of WAT is the storage of energy as it maintains high levels of triglycerides. BAT, on the other hand, produces mainly heat, and therewith induces thermogenesis when needed.<sup>168</sup> Beige fat can act as WAT or BAT, and depending on the stimulus it can store energy or increase mitochondrial activity to produce heat.<sup>170</sup> WAT is an endocrine organ secreting important hormones involved in food regulation, such as leptin and adiponectin. In obesity, secretion of these hormones is dysregulated, with leptin being

increased and adiponectin decreased.<sup>68</sup> Adipose tissue also secretes serum amyloids A (SAA) and plasminogen activator inhibitor 1 (PAI-1) which inhibits anticlotting factors and is highly associated with thrombosis.<sup>171</sup> PAI-1 is associated with visceral fat depots but not with subcutaneous fat in humans.<sup>39</sup> In women, WHR is associated with carotid intima-media thickness (CIMT) decrease, indicating that visceral fat is related to atherosclerosis.<sup>26</sup> The correlation between CIMT and visceral fat remained significant after BMI and total fat correction. Additionally, a correlation was found between flow mediated dilation (FMD) and abdominal fat size.<sup>172</sup> Other pro-inflammatory cytokines, such as SAA and angiotensinogen have been associated with an impaired cardiovascular system, and are thought to be involved in the development of hypertension, atherosclerosis and thrombosis.<sup>3,171,173</sup> Altogether, it is clear that increased adiposity, depending on the fat depot, has many consequences for human health.

Evidence revealed that impaired visual recognition memory and memory flexibility were associated with visceral adiposity and HFD-induced weight gain in Black 6 mice.<sup>87</sup> In humans, similar results have been found. Elevated adiposity was associated with impaired working memory and cognitive flexibility in young adults.<sup>55</sup> Moreover, total fat percentage was negatively associated with visual memory and visuospatial skills in young healthy obese men,<sup>47</sup> suggesting that adipose tissue can influence cognitive function.

In obesity, adipocytes become hypertrophic, which changes their secretory profile and induces low-grade inflammation. Inflamed adipocytes secrete various inflammatory cytokines and chemokines such as IL-6 and TNF- $\alpha$ .<sup>174</sup> These cytokines can activate and mobilise macrophages, but also recruit dendritic cells and B cells.<sup>175</sup> Leptin is also able to increase expression levels of IL-6, IL-1 $\beta$ , and TNF- $\alpha$  in vitro.<sup>108</sup> Altogether, this contributes to low-grade systemic inflammation, which is a hallmark of excess fat depots. Cytokines and free fatty acids can translocate through the BBB, stimulating immune cells in the brain, such as microglia, and thereby induce neuroinflammation. Moreover, systemic inflammation alters the BBB integrity, which increases peripheral immune cell infiltration and further exacerbates neuroinflammation.<sup>176</sup>

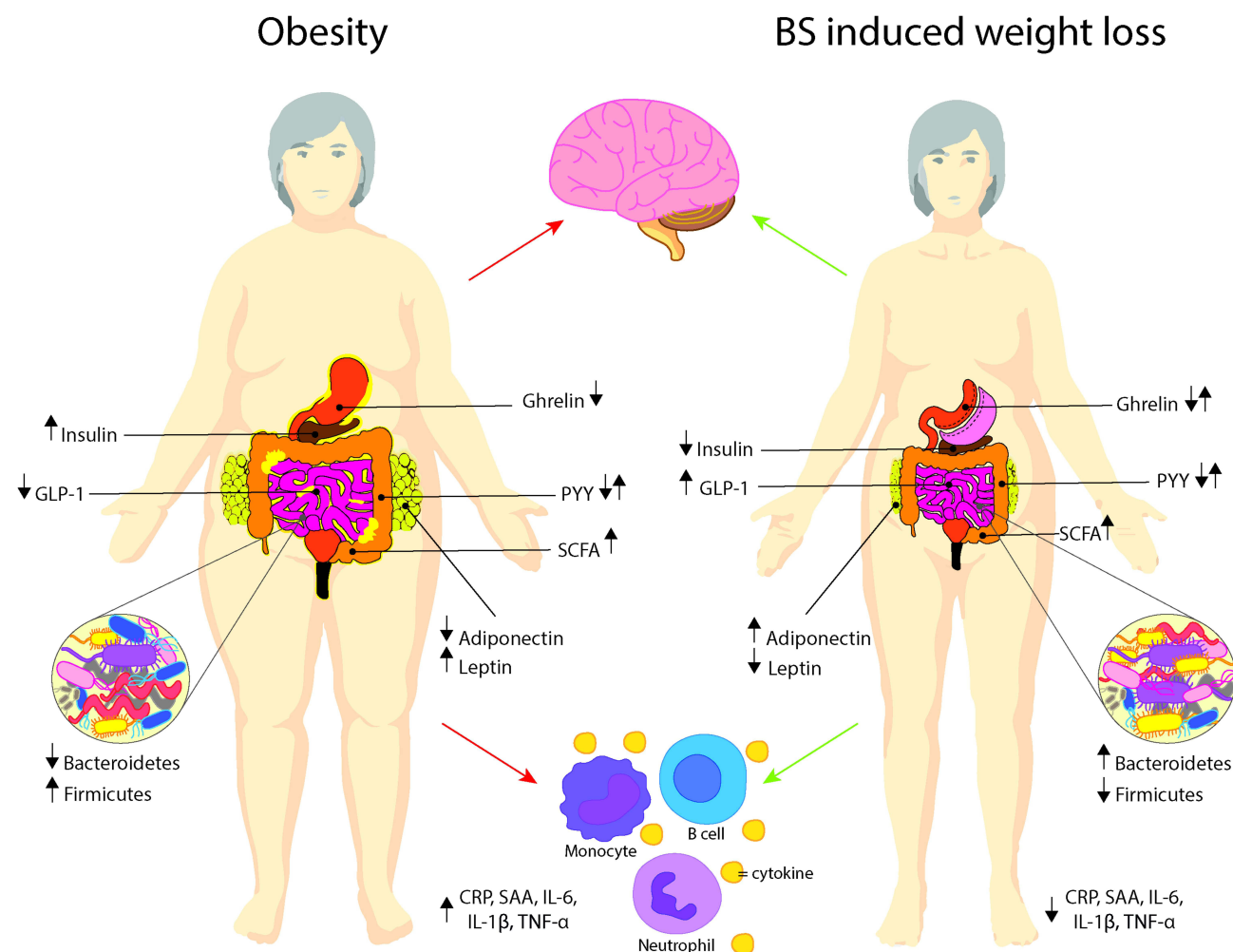
As shown by magnetic resonance imaging, reduction in abdominal WAT is mainly responsible for BS-induced weight loss, followed by liver and pancreatic fat, whereas no changes in BAT have been observed.<sup>56,57</sup> The significant reduction in visceral adipose depots after BS also partially reversed the prothrombotic state seen in obesity.<sup>39</sup> Laparoscopic adjustable gastric banding or gastric bypass improved both functional and structural markers of atherosclerosis, in terms of CIMT and FMD measures. It is speculated that the cardiovascular pathologies are a multifactorial problem, which can be improved by lower levels of visceral fat and subsequent improvements in adipokine and cytokine secretion, instead of weight loss alone.<sup>172</sup> After BS, obese sprague Dawley rats showed tissue weight loss and increased adiponectin expression levels, which upregulated the expression of sirtuin 1 and therewith increased WAT browning.<sup>89</sup> Serglycin (SRGN) is a dominant proteoglycan in inflammatory cell types that infiltrate WAT in the context of obesity.<sup>93</sup> In both mice and humans, SRGN is accompanied by higher expression levels of several inflammatory markers, albeit it is demonstrated that fat loss after BS can reduce mRNA expression levels of SRGN and inflammatory genes (including macrophage markers).<sup>93</sup> Furthermore, *Srgn*<sup>-/-</sup> mice demonstrated decreased levels of proinflammatory M1 macrophages and crown-like-structures, a hallmark of adipocyte driven inflammation, compared to *Srgn*<sup>+/+</sup> mice after sugar and fat-induced obesity.<sup>93</sup> These findings suggest that SRGN is associated with adipose tissue accumulating immune cell populations under obese conditions, which can be restored after BS. Finally, lower inflammatory makers (eg CRP, SAA, TNF- $\alpha$ , IL-1 $\beta$ ), lower leptin and increased adiponectin levels were observed in humans 6 months after Roux-en-Y gastric bypass.<sup>11</sup> In summary, these results indicate that BS can restore adipose tissue functionality and thereby might improve obesity-related comorbidities.

Despite all positive effects of BS discussed in this review, one should also be aware of the negative consequences. BS can induce post-operative gastrointestinal complications and thereby reduce the quality of life, but also vitamin and nutritional deficiencies have been observed in post-BS individuals.<sup>177,178</sup>

## Conclusion

A growing body of evidence reveals that obesity is related with alterations in neuroendocrine production and secretion, including ghrelin, insulin, GLP-1 and PYY (Figure 1). These alterations increase food intake and reduce insulin sensitivity, leading to increased adiposity and the development of T2DM. Obesity is also associated with a dysbalanced gut microbiota





**Figure 1** Changes in body composition and hormones after bariatric surgery. Insulin, leptin and various short-chain fatty acids are increased, while ghrelin and adiponectin are decreased in individuals with obesity compared to lean controls. Levels of PYY have been shown to be higher, lower or unaltered in obesity. After bariatric surgery all these endocrine and insulin levels improved in comparison to pre-surgery patients. Obesity also has negative effects on inflammation. Multiple immune cells are involved in obesity driven inflammation, such as macrophages, T-cells, cytotoxic cells, among others. Increased cytokines and low grade systemic inflammation are a hallmark of obesity and may cause alterations in cognition and brain structure. Bariatric surgery seems to improve both these factors on a global level.

**Abbreviations:** GLP-1, glucagon-like peptide 1; PYY, peptide YY; SCFA, short-chain fatty acids; CRP, C-reactive protein; SAA, serum amyloid A; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor.

and consequently with an impaired metabolite profile, which can increase gut barrier permeability and low-grade systemic inflammation. Finally, obesity is linked to dysfunctional WAT, leading to changes in adipokine and cytokine secretion profiles. The aforementioned effects can alter human health in distinct ways, and through direct or indirect pathways can promote the development of obesity-related comorbidities as well as cognitive impairment. Luckily, BS is an effective treatment for obesity. It decreases body weight not only due to physical effects such as reduced food intake and malabsorption but also due to the various neuroendocrine changes which affect energy homeostasis and hunger/satiety. Moreover, BS might improve the gut microbiota diversity and restore WAT function, which can improve obesity-related immunological and cognitive impairments. However, future research should focus on the long-term effects of BS, to be able to investigate the neuroendocrine, microbiota and WAT changes and to potentially determine the new “normal” after homeostatic adjustments. Various studies have focused on neuroendocrine alterations already after six months. Six months post-surgery patients lose weight rapidly and generally still follow their post-operative diet. Therefore, the observed effects 6 months post-surgery might differ at longer follow-ups, when patients achieve a stable weight, or regain weight. To summarize, BS is a good procedure to treat obesity and its related pathologies, however long-term effects remain unsolved. Future studies should focus

on long-term effects after BS and try to determine potential factors (eg gut microbiota and hormones) that are involved in successful weight loss after surgery.

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