Microbiota and Immune/Semiochemical System

Subjects: Microbiology

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The expression microbiota-gut-brain axis is well recognised nowadays (alongside the related terms microbiome-gut-brain axis and, occasionally, brain-gut-microbiota axis), however it is also clear that the action of the microbiome includes an immune system component. In turn, any concerning reaction from this system will necessarily involve the brain in fashioning a coordinated response, such as is seen in the case of traveller's diarrhoea, for example. The interaction of the microbiota with the body is therefore bidirectional: with the gut wall itself and with the immune system, both of which link through to the brain. Any chemical communication with the microbiome is actually semiochemical, in the sense of the transfer of signalling information between the Kingdoms of Life, i.e. prokaryote to eukaryote and *vice versa*. Accordingly, the two terms "microbiota-gut-brain axis" and "immune/semiochemical system" should be considered alongside one another.

microbiota microbiome microbiota–gut–brain axis non-communicable diseases prebiotics probiotics semiochemicals ingestible sensor

1. Introduction: The Unstoppable Rise of Obesity

By the late 20th century, it was clear that dietary and behavioural treatments for the control of obesity were failing [1] and yet, interestingly, the accumulated evidence pointed to the idea that people were following the recommendations of the time and were, indeed, eating less than had been normal in earlier years, at least in Britain [2]. By the early 21st century, experiments involving heavy isotope labelled water confirmed that levels of physical activity of people were similar in distinct parts of the world, were about what could be expected for similar-sized mammals and, moreover, had not undergone notable change since the 1980s [3]. As no new ideas were available at the time, there was little to do except bemoan the failure of these "biology and genetics" approaches [4], to recognise that the field is full of unsupported assumptions, indeed plain guesses [5], and to count the substantial cost of the obesity crisis [6]. Needless to say, levels of obesity continue to rise across the world [7], along with a worryingly rapid drop in strength, especially noticeable in schoolchildren, as reported both in England [8], and in Slovenia [9].

However, alongside the essentially thermodynamic studies of the late 20th century, there was an increasing interest in the bacteria inhabiting our intestine. One observation caused an immediate stir, that obesity could be transferred as if it were an infectious disease, at least among the microbiota of mice [10]. Unfortunately, this apparent lead turned out not to be useful, and it remains possible to study aspects of obesity without any reference

to the microbiome whatsoever [11]. Alongside these deliberations, however, the existence of the microbiota–gut–brain axis was noted when its degradation became associated with obesity [12]. Interestingly, Denis Burkitt strongly suggested early on that elevated levels of dietary fibre reduced the levels of non-communicable disease, including obesity (see discussion, below) [13]; and although his suggestions were not fully borne out in practice, his dietary fibre hypothesis has been given renewed emphasis by observations about the production of the energy-supplying short chain fatty acids acetate, propionate and butyrate (SCFAs) within the microbiome under the influence of high-fibre diets [14]. Although these leads are still being pursued, Burkitt nevertheless also noted that the cattle-rearing Maasai did not eat a high-fibre diet and yet remained healthy, in his day at least [13].

By contrast, researchers' own work suggests that the mutualistic microbiome behaves as a combination of immune and messenger chemical (semiochemical) systems stemming from the Precambrian Vertebrata. The presence of non-communicable disease further suggests that it has been damaged by the use of caesarean section and by biocides, including heavy metal pollution [15], and that the damage is increased from one generation to the next in an ongoing “snowball effect” following transfer of a malfunctioning microbiome in the apparently accidental process that researchers have termed *maternal microbial inheritance* [16].

Note that, while the term “microbiota” is a consortium of microorganisms including bacteria and archaea, fungi (mycobiome), and viruses (virome) that have evolved to live cooperatively in each ecosystem, for example, inside human body, the term microbiome includes both the symbiotic microorganisms and their genes with beneficial characteristics; microeukaryotes are present in the microbiome and are assumed to play a significant role but are not adequately defined as yet. However, researchers use the two terms microbiota and microbiome interchangeably, primarily to avoid repetition and to smooth the flow of discussion. Overall, the focus of this entry is on the microbiome as a “black box”, in which the key point is the output of the microbiota, rather than the complexity of the system within the intestine itself.

2. Health versus Pollution: The Degraded Microbiome

The earliest metagenomic analyses of the human microbiome was carried out on two reportedly healthy adults using the 16S ribosomal DNA sequences, illustrating the diversity of microbial form and function that researchers now take for granted [17], obsoleting the idea that all microbes are malignant *per se*. Interestingly, of course, researchers now know that greater microbial diversity is associated with health [18][19], bringing into question the concept of what exactly constitutes a “healthy adult” in the first place, and also of what a human being is constituted, because human attributes combine with the result of the metabolism of millions of microbes [17] in the mouth, throat, nose, skin, vagina, saliva, and intestines [20]. e focused on guts because there is located the largest sensory organ of the human body [21], and the bidirectional communication between the intestines and the brain, the microbiota–gut–brain axis, possibly arose long time ago during the Precambrian Vertebrata [15].

The Yanomami, a people living in the Venezuelan–Brazilian Amazon, are among the healthiest in terms of their blood lipid profiles, with no sign of obesity, at least until they leave their communities and enter what can loosely be termed the “modern world” [22], suggesting that “westernisation affects human microbiome diversity” [23]. Likewise,

the Tsimane, from the Bolivian Amazon, not only show low levels of cardiovascular disease [24], but also little dementia, despite their high systemic inflammation [25]. Lest people think that this is unique to South America, the Hadza, a people from Tanzania, were similarly healthy and, moreover, were found not to carry any strains of Bifidobacteria [26], a group of microorganisms currently held to confer health benefits [27], albeit not very successfully [28].

In the mid-20th century, Denis Burkitt studied the health gap between what he called “Modern Western Civilization” on the one hand, and traditional African societies on the other, finding a host of non-communicable diseases among the former that were simply absent from the latter [13]. Having discerned an environmental cause, and knowing nothing of the microbiome, he then went on to surmise that the low levels of fibre in modern foods stood for a form of dietary deficiency. However, not only could he not connect the inflammatory forms of non-communicable disease with dietary fibre, but he also reported that the cattle-rearing Maasai (Masai in his day) were free from such disease, despite their relatively low fibre, modern-type diet [13]. By contrast, the epidemiology of many non-communicable conditions is more consistent with selective poisoning of the microbiome by the pollution associated with industrialisation, leading to disease following a deficiency of microbiome function [29]. It is likely that this microbiome–body relationship was first developed in the Precambrian Vertebrata, and that the disconnect between microbiome and gut is due specifically to heavy metal poisoning [15]. Accordingly, it follows that no one born in a polluted environment can be considered safe from non-communicable disease [15]; by following this argument, there is no absolute definition for the term “healthy adult”. In terms of the potential for disease, the mantra must be “guilty until proven innocent”.

3. Genes versus Environment: Maternal Microbial Inheritance

While it has always been realised that the action of our genes must, somehow, be modified by factors within our environment, more attention has been paid to the former, with its readable sequences and theoretical opportunities for modification, but the precise significance of the term “environment” has been left in abeyance. Regarding obesity, Claude Bouchard and his team performed an experiment in the 1980s in which twelve pairs of young adult genetically identical twins were over-fed by 1000 kcal per day above their normal baseline food intake. Prior to the experiment, neither the twins themselves, nor their parents, showed any sign of excessive adiposity or specific lipid-related diseases. Over 100 days, all the twin pairs had gained weight, but each pair, though similar within themselves, were very different from one another [30], these results were presented in terms of their genetics. At about the same time, David Barker was developing his hypothesis by stating that the nature of non-communicable diseases in adults, including schizophrenia, could be traced back to their childhood, or even into the womb itself [31]. Although much speculated on [32], and economically literate [33], this “fetal origins hypothesis” has never been fully accepted. Researchers' suggestion is that the microbiome of the mother represents a part of the overall environment in which the individual genetic code of the child operates. Epigenetic mechanisms for temporary deactivation of protein synthesis have been known since the mid-20th century [34], but more recently, there have been investigations into the existence of heritable epigenetic mechanisms [35], but not without debating the viability of the available evidence [36]. Of course, such questions would be answered if the microbiome inherited from the

mother were capable of epigenetic control over aspects of the development of the child. As yet, however, there is little known about the ability of bacteria to exert control over genetic processes [37], let alone any skills obtained by the uptake of mobile genetic elements or, indeed, those conferred by unicellular eukaryotes [15].

As with Burkitt's findings discussed above, nobody knew about the microbiome, nor that it was being transferred from mother to child by the seemingly accidental process of maternal microbial inheritance [16]. Of course, twins are born at the same time from the same mother so, accordingly, the outcome of Bouchard's experiment [30] would have been affected by both their somatic gene sequence and, also, the genes belonging to their microbiota. While this accounts for the intra-pair similarity, in a sense the microbiome stands for a factor associated with the environment, as the inter-pair variability shows a significant prior influence on the mother, such as may be associated with antibiotic treatment, for example. Similarly, in principle this accounts for Barker's epidemiological observations about the source of adult disease, albeit in the modified form of an "infant origins hypothesis" [31]. Interestingly, the presence of significant differences *within* genetically identical twin pairs may, perhaps, be attributable to differential microbial contamination following delivery by caesarean section [38], or simply differences in their adaptive immune system [39].

A similar argument applies to the findings of David Strachan, in which immune system malfunctioning in the infant will lead to future problems such as asthma and hay fever [40]. While Strachan's original "hygiene hypothesis" has been followed up by Rook and co-workers, still no trace of an *external* immune system training agent has been found [41]. Nevertheless, the possibility remains that the fully functioning microbiome carries an *internal* agent which enables the calibration of the immune system against the microbial environment of the mother. Such an agent could represent a so-far hypothetical microbial equivalent of the dendritic cells of our own human immune system [42], which researchers have previously described as microbial sentinel cells [43], and suggested that they may stem from the Precambrian Animalia [15].

4. The Mutualistic Microbiome: External Microbes and Their Antigens

Of course, all foods are closely associated with potentially pathogenic microbial contamination and, while cleaning and disinfection may reduce the microbial load [44], even cooking still leaves certain genetic sequences more or less intact [45]. Presumably these microbial fragments include plasmids and other mobile genetic elements that can become incorporated into the functioning microbiome and, in turn, can be passed on to the neonate in preparation for the microbial world it will soon inhabit as an independent entity [15]. While weaning a child onto solid foods is usually achieved relatively easily, an adult eating uncooked food in a foreign environment may suffer from dramatic consequences [46]. Although the causative agents of traveller's diarrhoea are the commonly called pathogens, of course they have no effect on people originally brought up in those countries. Needless to say, as these conditions are unpleasant but rarely life-threatening, to researchers' knowledge there has been little research on the possibility of adults themselves becoming immune to this whole new set of microbes. Instead, assuming the worse effects are avoided, it is interesting to speculate as to whether this probiotic-like immune stimulation of the microbiota–gut–brain axis can actually contribute to the enjoyment of the overall experience of foreign travel.

Significantly, however, it is worth noting that most of the microbiome-related work has been conducted on the degraded microbiome, as described above, and focuses virtually exclusively on the prokaryote constituents. Although the relative absence of work on the potentially critical microeukaryote components of the microbiome has been noted [47][48], there are exceptions, such as a study on the early development of the human mycobiome [49]. Of course, the ability of *Toxoplasma gondii* to influence the brain of a mammal illustrates the potential organising ability of unicellular eukaryotes [50]. Although, as with *T. gondii*, such species are almost invariably treated as parasites, it is noteworthy that *Blastocystis* species are commonly observed in apparently healthy individuals [51] and can pass between different animal species relatively easily [52]. Nevertheless, if one role of hypothetical microbial sentinel cells is to seek out novel antigens to effectively calibrate the immune system of the child compared to that faced by the mother, it could be that such cells are simply no longer present in populations chronically exposed to heavy metal pollution [15].

Although there is currently no reason to assume that traveller's diarrhoea is altered by microbiome-function deficiency disease, it is worth mentioning that the whole spectrum of allergic and autoimmune diseases could come within its range. Significantly, the first comprehensive description of what researchers now know as seasonal allergic rhinitis was by John Bostock in the early 19th century [53], at about the time when Burkitt mentioned descriptions of obese people becoming common in art and literature [13]. Thinking that he was on to something important, Bostock continued his search for people with unambiguous symptoms, eventually uncovering a grand total of 28 from all over the British Isles. Compare this with the situation in Britain in recent times, with a report of 21% of schoolchildren taking medication in 2005 [54]. While hay fever is itself trivial, of course there is a relationship with food allergy [55] and atopic disease in general [56]. Although he could not have understood its significance, Bostock stressed that the sufferers were "all from the highest ranks of society" [57], and it is probable that their mothers were using heavy metal-based cosmetics [58], thus condemning their children to the sort of diseases researchers are familiar with today [29]. While the symptoms of hay fever are unmistakable, the same cannot be said for mental illness and, when faced with such problems among rich people in 19th century Vienna, Sigmund Freud had no precedent to fall back on. Although psychoanalysis eventually became respectable [59], of course it was never fully accepted. Indeed, it is telling that Burkitt's otherwise comprehensive review never mentioned mental health at all [13].

5. The Mutualistic Microbiome: The Immune/Semiochemical Complex

Rather than consider all the interactions between the different microbes both with one another and with the gut wall, it is more valuable to consider the microbiome as a "black box", an object whose internal workings are a still an intricate mystery but whose output is significant [60]. During the initial investigations, it was noted that so-called germ-free mice exhibited an unnatural stress response [61]. As noted in the Introduction, in due course the term microbiota–gut–brain axis has become recognised as a significant component of the healthy body due, at least in part, to its association with obesity [12]; on the other side, individuals with anorexia nervosa manifest a reduction in microbiota diversity and there is a significant association with depression, anxiety, and lack of appetite [62]. It seems

that there are two classes of significant chemical output from the microbiome: molecules associated with energy supply on the one hand, and interkingdom signalling molecules, semiochemicals, on the other. Note that, by this definition, any bodily hormones or related chemicals sending signals to modify the behaviour of the microbiome are also semiochemicals.

In reporting his African studies, Burkitt emphasised that a substantially greater faecal weight, indeed as much as three-fold, was associated with the absence of non-communicable disease [13]. Interestingly, it has been reported that greater stool microbial diversity has been associated with a higher level of gut motility, presumably implying that signals from the microbiome (psycho-active substances such as dopamine, serotonin, and catecholamines) improve peristalsis [63].

Signalling molecules have been described as being produced in the gut lumen, including the catechol dopamine [64], which has a role in controlling aspects of the immune system [65]. Dopamine generated within the brain has also been shown to affect systemic glucose production, possibly as a part of the overall microbiota–gut–brain axis [66]. In a similar fashion, while the microbiota produces both energy-related B-vitamins and the short chain fatty acids (SCFAs) acetate, propionate, and butyrate [67], these latter compounds contribute to the production of serotonin [68], as well as aspects of the immune system [69]. Accordingly, all these molecules can be classed as part of the dual immune system/semiochemical output of the mutualistic microbiome [70]. Interestingly, it seems that the ability to synthesise these key semiochemicals could have been passed on from bacteria to animal cells by horizontal gene transfer at some stage during their evolution [71].

6. Breaking the Contract: Dysbiosis as Microbiome Failure

While the name “dysbiosis” seems an excellent shorthand for a malfunctioning microbiome, the term is imprecisely defined [72]. Likewise, Harald Brüssow has pointed out that there is a need for more investigation into causal relationships between specific bacterial commensals and disease states, within a “sound ecological and evolutionary” rationale [73]. Researchers' own suggestion is that there is essentially no connection between specific bacteria and disease, rather it is the inability of the depleted microbiome to support mobile genetic elements that is the critical factor [16]. In support of this thesis, researchers further suggest that the rationale for the microbiome is to add the flexibility of horizontal gene transfer at the microbial level to the relative stability of multicellular evolution by the inheritance of acquired characteristics, thus combining the benefits of operating both above and below what has been called the Darwinian threshold [74]. Note that the failure of the microbiome is at an evolutionary level, albeit that this failure is reflected in a myriad of seemingly different conditions [75]. Of course, this is closely analogous to the holobiont concept pioneered by Lynn Margulis [76][77][78]. Nevertheless, it is both the nature and the timing of the non-communicable diseases resulting from the breakdown of mutualism that supplies the best sign as to the role of the fully functioning microbiome prior to its degradation.

In the light of Barker’s original observation of the “fetal and infant origins of adult disease”, it seems likely that both the immune system and the microbiota–gut–brain axis start to develop immediately after birth [75], and that any lack of microbial function will have a negative impact on the eventual health of the individual, to a greater or lesser

extent [29]. The concept of mutualism implies two parallel interactions that benefit both components. Thus, while the microbiome guest calibrates the immune system of the neonate against the microbial environment of its host mother, the adult must, in turn, respond by supplying nutrition to its microbial guest ready for the next generation [15]. It is important to note, however, that this host–guest relationship must be sufficiently flexible to cope with the expected events of life: accident and illness; famine and, of course, the special conditions of pregnancy [79]. Although the details are not yet clear, it is possible to imagine the microbiome providing a steady level of semiochemical-delivered demand for nutrition, balanced against a variable hormone-delivered demand from the body. If so, any inclement conditions may lead to an increase in hormone-delivered demand followed by microbiome shutdown until conditions improve. Researchers' suggestion is that the mutualistic microbiome operates across the generations as illustrated in **Figure 1** [15].

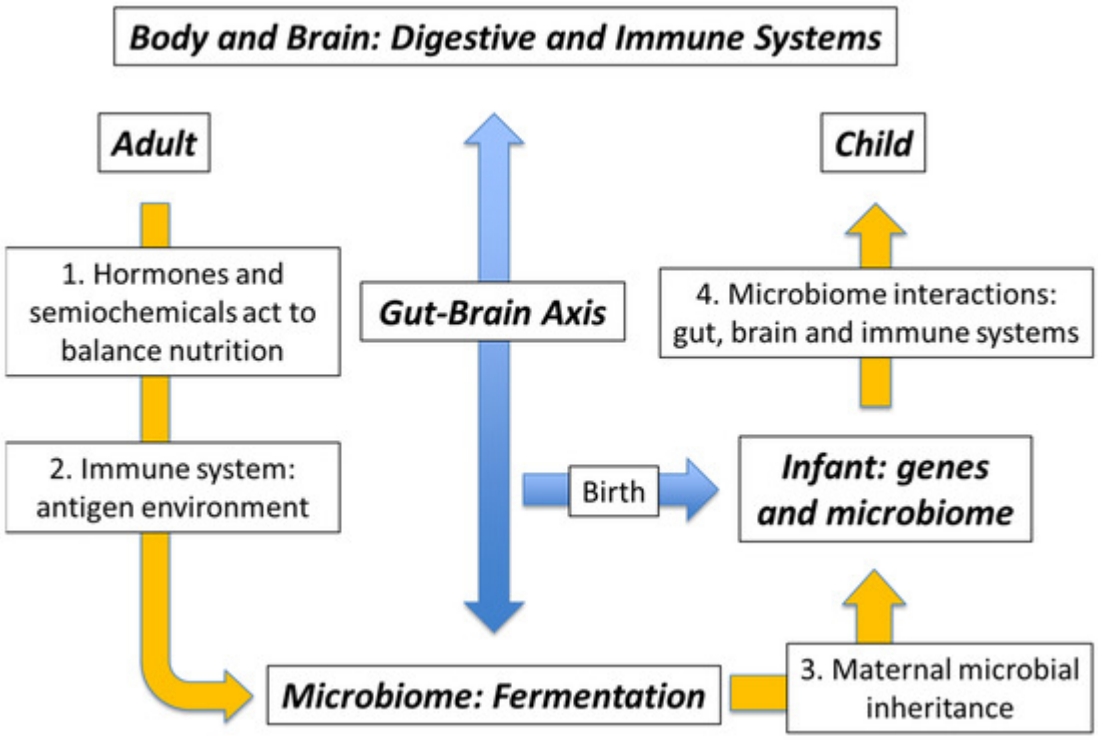

Figure 1. Semiochemical/immune complex: Adult and child.

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