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Intestinal microbiota and its host: harmony or discord?

Role of the gut microbiota in psychiatric diseases

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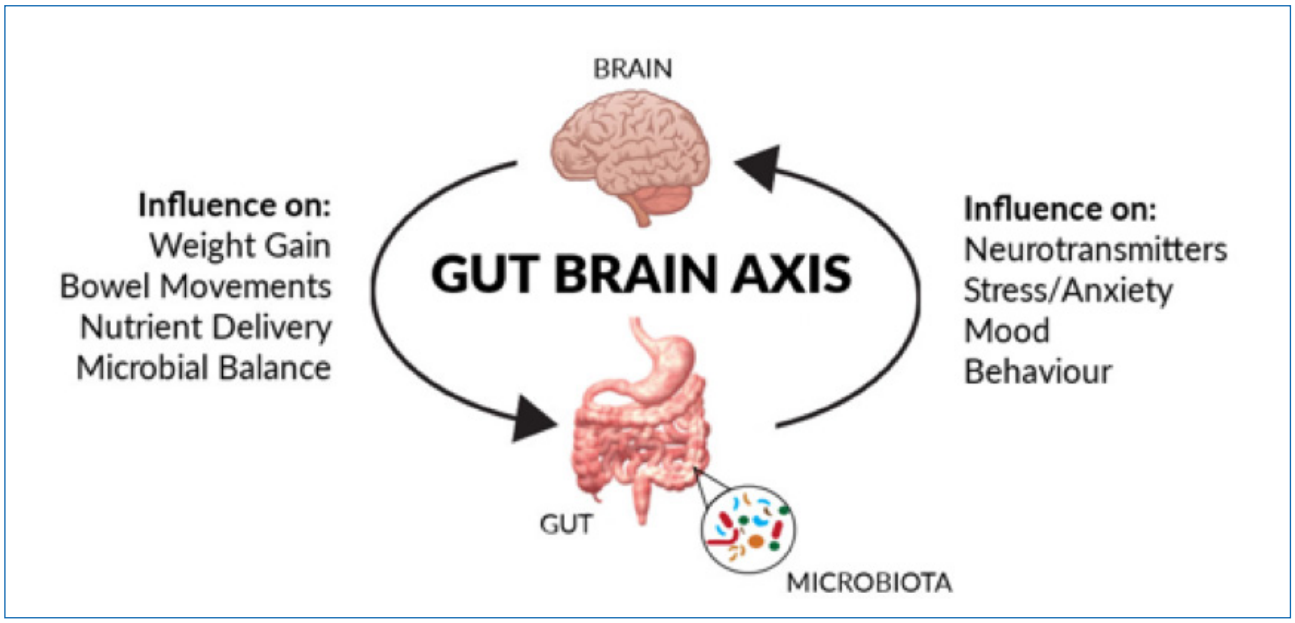
INTRODUCTION

A strong relationship between the gut microbiota and the development of psychiatric diseases, generating a gut-brain axis, is commonly recognized today.[1,2] The influence of brain on the gut has been observed in weight gain and nutrient intake as in the maintenance of microbial balance. Conversely, the intestine has shown its influence on neurotransmitters, stress, mood and behavior (Figure 1).[3]

Which arguments support such connection between the gut microbiota and psychiatric diseases, and in which pathologies has an interaction been observed? Alcohol-related disorders, in particular, are a perfect illustration of the gut-brain relationship.

Figure 1. Functional interactions between gut microbiota and host metabolism. Characteristics of the intestinal microbiota favoring obesity and insulin resistance.[3]



THE INTESTINAL MICROBIOTA AND THE DEVELOPMENT OF PSYCHIATRIC DISORDERS

Psychiatric illnesses are commonly understood to be the effect of an interrelation between a series of biological factors, psychological elements that are present in the individual, including in his or her history, and contact with the community. Early life events of the individual, as well as the quality of social interactions, play a key role in the development of a psychiatric disorder. Thus, the effects of early traumatic events may be contradicted by a good quality of social relation or, on the contrary, aggravated by factors such as social rejection or stigmatization. Besides, events occurring in the individual's life, especially those of his or her early life, are recognized today as a crucial factor in the development of the immune system.[4,5] In fact, the immune system has a major role in both the central nervous system and communication in the brain.[6]

All of these various interactions have to be taken into account when considering the development of psychiatric diseases and provide an explanation for the effects of the gut microbiota in this context.

THE ARGUMENTS

The arguments supporting a link between the microbiota and psychiatric diseases are of several kinds. They are essentially based on observations made in animal models (probiotic or transplant studies in axenic mice). Studies in humans are scarce. Nevertheless, findings from both types of study may be combined to help in understanding the role of the microbiota in these diseases.

Early exposure to stress

Exposure to stress has a major influence on the expression of gut microbiota. Exposure of the mother to stress, by inducing changes in the expression of the vaginal microbiota, leads to bacterial changes in neuronal expression in the offspring. It has also been shown that exposure to stress early in the life of an animal clearly induces behavioral abnormalities. These are associated with changes, both in gut activity and in the composition of the intestinal microbiota, which interfere with these processes.[7,8]

Early exposure to antibiotics

Similarly, some studies have shown that early exposure of the microbiota to antibiotic therapy has major effects on behavior. A recent study has examined in murine models the effect of early exposure to antibiotics of the same type as those usually given to young children.[9] The authors report that this exposure induced significant modifications in the expression of character, with difficulties of socialization in mice exposed to antibiotics, and even a form of hostility and combative behavior towards control mice.[9]

Cognition, emotions and social interactions

Numerous studies have also demonstrated, in humans as well as in animals, the important role of the gut microbiota in cognition, in the expression of emotions, and in social interactions. This phenomenon is observed especially in animal models.[10]

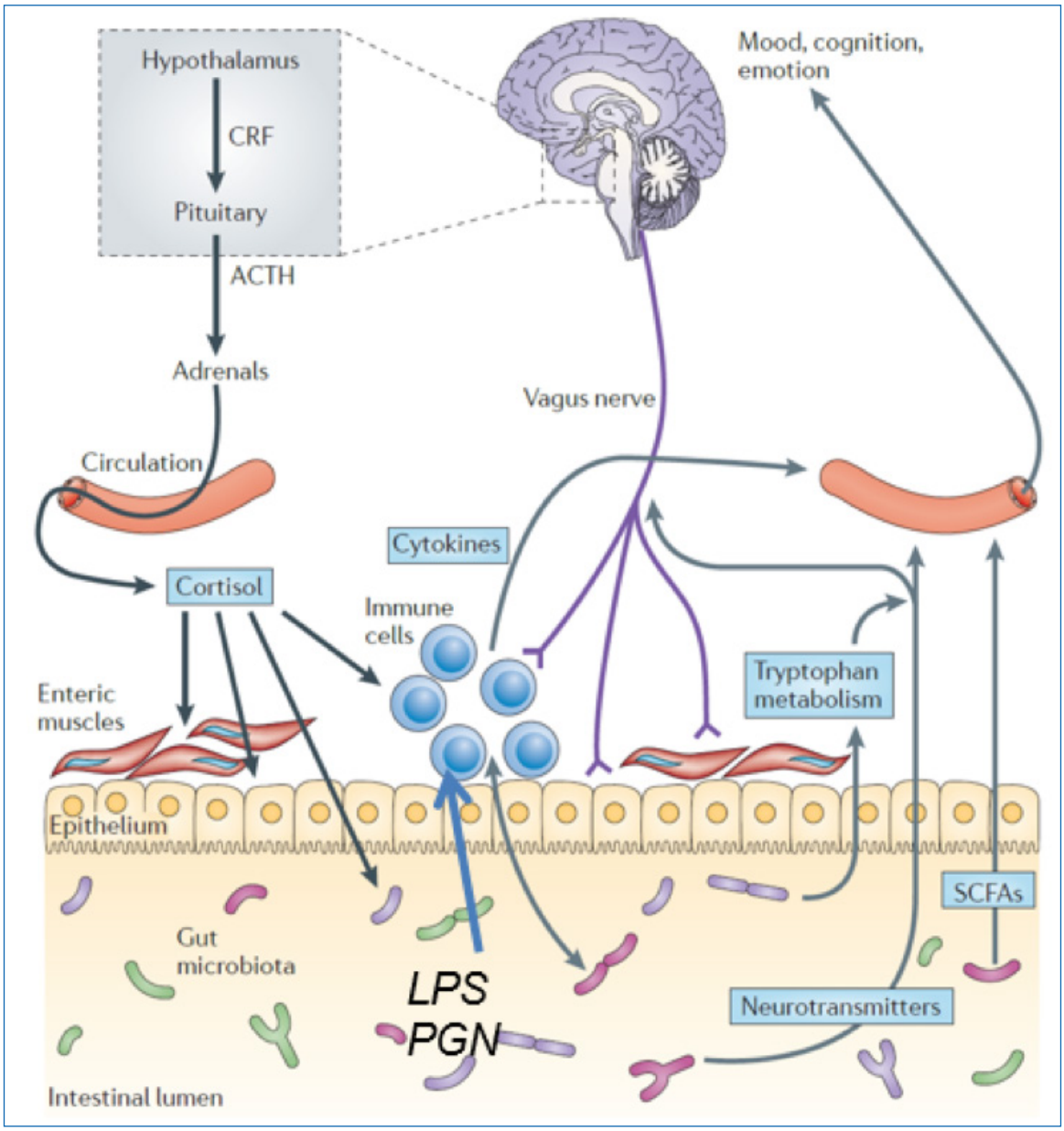
Gut-brain interactions: which pathways?

Different pathways have been identified as being involved in the communication between the gut and the brain, explaining the intestinal-brain interactions (Figure 2).[11] The factors involved in the process are:

1) microbial molecules such as short-chain fatty acids (maturation and function of microglia), AhR ligands (astrocyte function), microbial-associated molecular patterns (LPS and PGN), which stimulate the inflammatory pathways, and the tryptophan metabolites of which synthesis depends on the activation of inflammatory pathways;
2) neuroactive molecules (neurotransmitter intestinal biosynthesis and regulation of neuro-transmitter signaling);
3) neuronal signaling (stimulation of the vagus nerve).

Fung et al[12] recently published a review of studies on the gut-brain axis in humans and animals. All of the different pathways identified as explaining the relationship between the gut and the brain are presented, demonstrating the crucial role of gut microbiota in the orchestration of brain development and behavior.[12] The authors emphasize the importance of the immune system as a regulator of these interactions.[12]

Figure 2. The Gut-Brain axis[11]



WHICH DISEASES?

Autism spectrum disorders are the most frequently studied, with the greatest number of investigations. These have highlighted an important role of the gut microbiota in this context, with an effect on both mood and ability to socially interact.

The expression of **anxiety symptoms** has also been studied in animal models. The axenic mouse shows less sensitivity to anxiety situations and resistance to learning. Conversely, transplanting the microbiota from a mouse with an anxious phenotype to a mouse lacking this phenotype results in a transfer of the anxious behavior in the transplanted mouse.[13]

In **disorders related to post-traumatic stress**, it has been noted that in childhood, as in adulthood, exposure to stress leads to significant changes in the composition of the gut microbiota, attesting to the role of the microbiota in the development of this symptomatology.[14]

Few works have been performed in **schizophrenia**. Nevertheless some studies have shown the effect of the bacterium *Toxoplasma gondii* on the expression of this important illness.[15]

The role of the intestinal microbiota in **depression** has been shown in some research studies. The role of inflammation, in particular, has been identified in the expression of mood, with the observation of what has been referred to as "sickness behavior". This concept refers to the occurrence of an inflammatory reaction in the brain, in a person exposed to a series of immune factors. This inflammatory reaction leads, beyond the usual reactions of fever and activation of the hypothalamic-pituitary-adrenal axis, to a series of behavioral changes that strongly mimic the behaviors observed in depression. When the inflammation becomes chronic, it participates in depression.[16]

PROBLEMS RELATED TO ALCOHOL CONSUMPTION

Disorders related to alcohol abuse have been studied in three trials conducted in humans, aimed to assess the origins and role of peripheral inflammation in alcoholic disease and identify the transmission pathways.

In the first study, conducted in a population of alcohol-dependent patients, there was evidence of an increased intestinal permeability. This was associated with increased plasma LPS and activation of inflammatory cytokines that correlated with symptomatic manifestations of alcohol dependence: depression, anxiety, and craving.[17]

The second study, conducted in patients at the beginning and end of alcohol withdrawal, assessed the inflammatory activity from peripheral blood mononuclear cells.[18] This analysis, which resulted in complex findings, shows: **1)** that LPS and peptidoglycan pathways are activated in alcohol-dependent patients, **2)** that LPS pathway recover rapidly during weaning, unlike that of peptidoglycans which remained activated even at the end of weaning, indicating the existence of a recovery factor.[18]

In terms of clinical implications, these results indicate that the persistence of inflammation may predict the persistence of psychopathological manifestations of alcohol dependence. The best predictor of craving for alcohol was shown to be IL8, a chemokine secreted by the peripheral blood mononuclear cells.[18]

The third study compared two populations of alcohol-dependent patients, one with increased intestinal permeability and the other with normal intestinal permeability.[19] The authors observed that an important modification of a series of bacterial families and genera was associated with the increase of intestinal permeability. This change was associated with significant dysbiosis in this subpopulation, and to higher scores of depression, anxiety, and craving at the end of weaning, which may be important psychological factors of alcoholism relapse.[19]

These results in humans confirm the existence of a gut-brain axis in alcohol dependence, involving the microbiota in the intestinal barrier and behavioral disorders. They also suggest that the microbiota could constitute a target in the management of alcohol dependence.

A study in animal models was also carried out in this context. It included axenic mice and "humanized" normal mice (treated with antibiotics then transplanted with the fecal microbiota of alcoholic patients with or without alcoholic liver disease). The aim was to identify the causal role of the gut microbiota in alcoholic disease.[20] This study led to the discovery of a specific dysbiosis associated with the severity of hepatic alcoholic disease: mice transplanted with the microbiota of a severely affected patient developed more severe hepatic inflammation than those who received the microbiota of a subject free of liver disease. In addition, it was observed that in conventional mice humanized with the microbiota of a patient with severe hepatic alcoholic disease, a second microbiota transfer from a patient without liver disease improved alcohol-induced liver injury. Individual susceptibility to alcohol dependence and alcoholic liver disease thus appears to be very strongly related to the intestinal microbiota, suggesting the possibility of preventing and managing this illness by acting on the microbiota.[20]

COMMENTS, CONCLUSIONS

In human psychiatric diseases, supplementing patients with prebiotics (dietary fibers that can positively modify the intestinal microbiota composition) appears likely to improve both composition and activity of the gut microbiota. Prebiotics should act on the intestinal barrier, limiting its permeability and improving symptomatology. It could also have an effect on the immune system, reducing inflammation and neutralizing LPS. More particularly in alcohol-related disorders, from such beneficial effects, prevention of alcoholism relapse could be expected, a major problem in the management of these diseases.

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