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EDITORIAL

The visceral brain: Bipolar disorder and microbiota☆

El cerebro visceral: trastorno bipolar y microbiota

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Classically it is accepted that the brain is able to modulate different systems in the body, including the gastrointestinal system. The first direct observations date from the end of the 19th century and early 20th century, when emotional states were described as being able to alter the type of gastric secretion or intestinal regularity.[1] Nevertheless, this is not an exclusively one-way relationship, as chronic gastrointestinal conditions have been described that can affect us at an emotional level. The fact that the digestive system is the main producer of serotonin in our organism has to be taken into account, as it is responsible for more than 90% of its production. The intestines also have an extensive neuronal network that makes broad interconnectivity possible, and it interacts continuously with the central nervous system. This close relationship between the nervous and digestive systems has given rise to the concept of the ''gut-brain axis''. Our ancestors already intuited this concept, based on expressions that connect emotions and the digestive system such as ''having the stomach for something (or not)'' or describing something immoral, ignoble or revolting being ''stomach-churning''.

The digestive tract also contains a vast colony of microorganisms living in symbiosis with us, and their genome contains 100 times as many genes as the human genome.[2] This microbiota accompanies us from our mother's womb, and it varies as we grow until it stabilises at adulthood.[2] Under normal conditions the relationship between a human being and the approximately 100 trillion microorganisms in the intestinal microbiota is balanced and beneficial for both sides. This is so to the degree that, in studies of experimental animals with no intestinal flora, it has been shown that the microbiota is indispensible for the correct working of the immune and digestive systems, as well as for suitable control of the response to stress and anxiety,[3] as well as cognitive functions such as memory.[4] Likewise, it has been found that transplanting faecal material from patients with psychiatric disorders into rodents with no intestinal flora may induce psychiatric symptoms in these animals.[5] Due to all of these considerations, the appearance on stage of this influential actor has led to the concept of the ''gut-brain axis'' being broadened to the ''microbiota-gut-brain axis''.

As in all relationships, any attack on one party inevitably affects the others. Thus aspects of modern life such as new dietary habits, the massive use of antibiotics or continuous stress may alter microbiota composition and/or concentration, in what is known as dysbiosis.[6–8] Dysbiosis in turn, through transmitters produced by pathogenic microorganisms and through the vagus nerve, induces the activation of immuno-inflammatory processes and oxidative stress, as well as neuromodulating and epigenetic mechanisms.[9] All of these phenomena go on to affect the neuro-endocrine system as well as the hypothalamic-pituitary-adrenal axis and the central nervous system, influencing behaviour.[5]

In recent years the microbiota has therefore become an object of study in the pathophysiology of neuropsychiatric diseases, including bipolar disorder (BD).[10] In fact, BD was already associated with alterations in the immune system,

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although the cause for this was unknown, and dysbiosis is considered to be a possible mediator here.[2] This increases the paradigm shift that is occurring in psychiatry, where BD is no longer seen as simply an affective disorder caused by monoamine dysregulation, as it is now understood in the context of a dysregulation of axes, systems and communication routes, and definitively, of allostasis.[11] A new line of therapeutic options will surely open up based on the study of the microbiota-gut-brain axis, such as: probiotics, live microorganisms that, when ingested in suitable amounts, may benefit the health of the consumer; prebiotics, compounds that the organism cannot digest but which have a physiological effect in the gut by selectively stimulating the growth and activity of beneficial bacteria; or even antibiotic treatments such as Minocycline.[12]. These therapeutic alternatives have already been studied in diseases that are very common in our bipolar patients, such as obesity or cardiovascular complaints.

It would not have been possible to develop these new theories without the technological advances already made in the 21st century, as they made it possible to gain deeper knowledge about this axis. Metagenomic techniques now make it possible to study all of the genomes of the microorganisms in gut microbial ecology, even those that cannot be cultivated.[13] it is even possible to discover their functions and viability using metatranscriptomics.[13]

In spite of these advances, when talking of the microbiota-gut-brain axis we are still in unknown territory. We do not know the exact way in which the microbiota and CNS communicate, or the real influence of dysregulation on the working of the CNS or enteric nervous system. Moreover, study of this relationship is hindered by its dynamic and changing nature, which is easily modified by external factors. On the other hand, few studies have been performed in human beings, and the majority of the available information comes from animal studies. It is also hard to establish causal relationships, as the doubt always remains as to whether dysbiosis causes an affective episode or vice versa. Likewise, the fact must be taken into account that although some species of bacteria in our intestines are common to all human beings, the microbiota in each individual is unique.[14] This is important for diagnosis as well as for therapy, given that treatments must be adjusted to each patient, which once again shows the importance of personalised psychiatry.[15]

Apart from these limitations, major progress in this field surely means that answers will soon be found to these enigmas. Additionally, this new attitude to neuropsychiatric diseases is one more step in the increasingly holistic concept of the human body and its pathologies. This leaves Cartesian duality behind, in which the mind and body had very different essential characteristics. The moment has also come when we have to accept that, after everything, our reason is more visceral than we had thought.

Conflict of interests

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