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Review Article

Intestinal Microbiota and Alcohol Addiction

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Abstract: The involvement of the gut microbiota in various diseases, including psychiatric disorders, is increasingly being studied. We present here a review of recent data regarding the potential role of the microbiota in the development and maintenance of alcohol addiction. Changes in the composition and function of the gut microbiota have been observed in alcoholic patients. Several pathophysiological mechanisms explain the involvement of the microbiota in this addiction, including through the intestinal immune system, the production of psychoactive bacterial metabolites, or the alteration of intestinal permeability. Modulation of the microbiota through nutritional or pharmaceutical interventions is thus a promising therapeutic avenue for the management of alcoholism.

Keywords: Gut microbiota, dysbiosis, addiction, alcohol, gut-brain axis, therapeutic perspectives.

INTRODUCTION

Alcohol addiction is a major public health problem, responsible for significant morbidity and mortality worldwide [1]. Although the exact mechanisms are not fully understood, it is now accepted that alcohol addiction is a complex pathology affecting multiple physiological systems, including the digestive system [2].

Recent translational studies in humans and animals have highlighted the role of the gut microbiota in the development and maintenance of alcohol addiction [3, 4]. The intestinal microbiota refers to all the micro-organisms that inhabit the digestive tract [5]. Its composition may be altered (dysbiosis) in various pathologies, including addiction [6].

The aim of this update is therefore to define the intestinal microbiota, describe its composition in detail, explain its role in the body and in alcohol addiction, detail the underlying pathophysiological mechanisms and discuss the resulting therapeutic prospects.

The Intestinal Microbiota

The term "microbiota" refers to all the micro-organisms present in a given organ. We thus speak of oral microbiota, intestinal microbiota, vaginal microbiota, etc.

The intestinal microbiota, formerly known as the intestinal flora, refers to all the micro-organisms that colonise the digestive tract [5]. It is an extremely diverse population comprising mainly anaerobic bacteria, as well as viruses, fungi and parasites [7].

This microbiota is made up of around 100,000 billion (around 2 kg body weight) 21 bacteria belonging to more than 1,000 different species [7], 10 times more than the total number of cells in the human body [8]. Anaerobic bacteria predominate [8].

Metagenomic studies based on high-throughput sequencing of bacterial DNA have made it possible to classify the thousands of species that make up the intestinal microbiota into a few major bacterial families or genera [5]:

- Firmicutes, which are in the majority, include over 200 genera such as Lactobacillus, Clostridium, Enterococcus and Ruminococcus.
- The Bacteroidetes mainly comprise the genus Bacteroides.
- Actinobacteria include the genus Bifidobacterium.

- Proteobacteria include Escherichia, Enterobacter and Klebsiella.
- Verrucomicrobia includes the genus Akkermansia.

It is estimated that 2 phyla, Firmicutes and Bacteroidetes, together account for 90% of intestinal bacteria [9]. Their composition and balance are essential for various physiological functions in the host [2]. A disturbance in this balance, known as intestinal dysbiosis, is associated with a number of diseases, including chronic inflammatory bowel disease [2, 10], type 2 diabetes, alcohol addiction and some cancers [10].

The intestinal microbiota is as unique to each individual as fingerprints can be [11]. At birth, micro-organisms from faeces and the vagina are transmitted from mother to child during vaginal delivery. After a caesarean section, on the other hand, the infant's microbiota is inoculated with environmental microbes [12]. This initial colonisation triggers the development of the intestinal microbiota over the first three years, during which it diversifies and stabilises [13]. In adulthood, the composition of the microbiota remains relatively stable [14], until old age, when it undergoes a some depletion [15].

Many factors can affect the diversity and composition of the intestinal microbiota; age [14], genetics [16], some diseases and injuries [16] modulate the microbiota, but environmental factors such as medication (antibiotics, anti-inflammatories) [17], gastrointestinal infections [16] and lifestyle (unbalanced diet rich in fats, dietary changes, stress, smoking, alcohol) also have an impact on its diversity [16].

Role of the Intestinal Microbiota

The intestinal microbiota plays a fundamental role in the development and homeostasis of numerous physiological functions [18], such as:

- **Digestion**: The intestinal microbiota plays an active role in the metabolism of complex non-digestible carbohydrates (fibres), proteins and dietary lipids. It produces short-chain fatty acids (propionate, butyrate) used as a source of energy by the host [19]. It is involved in the synthesis of some vitamins (vitamin K, some B vitamins) and three essential amino acids: valine, leucine and isoleucine. It also regulates several metabolic pathways: absorption of fatty acids, calcium, magnesium, etc.
- **Intestinal barrier:** Bacterial products (short-chain fatty acids, polysaccharides) stimulate the production of antimicrobial peptides and mucus by intestinal cells. This barrier effect limits invasion by pathogenic micro-organisms [20].
- **Immunity:** The intestinal microbiota guides the development of the immune system by stimulating the production of intestinal lymphoid cells. It also confers tolerance to food and commensal antigens [21].
- **Gut-brain axis**: Numerous studies have demonstrated bidirectional communication between the gut microbiota and the central nervous system, paving the way for the concept of a "second brain" [22]. This connection involves the vagus nerve, bacterial metabolites (short-chain fatty acids) and numerous neuroactive and neuromodulatory substances (GABA, serotonin, dopamine, etc.) secreted by the microbiota and capable of influencing mood, emotions and cognition [23].

The microbiota has a close relationship with neurotransmitters (NTs), chemical messengers that transmit information between neurons via synapses [24]. The NTs most involved in the gut-brain axis are serotonin (5-HT), noradrenaline (NA), gamma-aminobutyric acid (GABA) and dopamine. The gut microbiota can regulate the expression of central and peripheral NTs and their receptors [24]. It also regulates intestinal NT synthesis in two ways:

Some bacteria produce them directly (in vitro), for example:

- Serotonin by the genera Candida, Steptococcus, Escherichia, Enterococcus
- Dopamine by the Bacillus and Serratia genera
- GABA by the genera Lactobacillus, Bifidobacterium

Or indirectly: most of the body's serotonin is secreted by intestinal enterochromaffin cells, requiring activation by short-chain fatty acids produced by intestinal bacteria [24]. Serotonin is then transmitted to the enteric nervous system by enteric neurons.

The microbiota also modulates the systemic immune and inflammatory response and affects the permeability of the intestinal barrier, with potential consequences for the integrity of the blood-brain barrier [25]. Disturbances in this balance, or dysbiosis, have been associated with numerous psychiatric disorders: depression, anxiety, autistic spectrum disorders [26], Alzheimer's disease [27] and addiction [28, 29].

Addiction to various psychoactive substances, such as alcohol, involves neuronal circuits and neurotransmitters in common with those regulated by the microbiota [30].

Role of the intestinal microbiota in alcohol addiction

Numerous experimental studies in animals and humans have demonstrated major alterations in the composition and function of the intestinal microbiota during chronic alcoholism [3, 31, 32].

It has been observed that the composition of the intestinal microbiota is altered in alcohol-dependent patients, with a significant decrease in Bacteroidetes and Firmicutes and at the same time an increase in Proteobacteria and Actinobacteria [33,34].

This dysbiosis is thought to play an active role in the behavioural effects of chronic alcoholism. Indeed, transplantation of microbiota from alcohol-dependent patients to axenic mice (i.e. initially devoid of any microbiota) is sufficient to increase the alcohol preference of these mice compared with mice transplanted with a healthy microbiota [28, 34].

The translocation of intestinal bacteria and their metabolites across an altered intestinal barrier plays a major role in the systemic inflammation and liver damage seen in alcohol-dependent patients [33, 34]. In addition to these digestive consequences, several pathophysiological mechanisms have been described to explain how these disturbances in the intestinal microbiota contribute to the development and maintenance of alcohol addiction, particularly via anxiety/depression and craving, which encourage relapse [35].

Pathophysiological Mechanisms

Several interconnected pathophysiological mechanisms have been proposed to explain the potentially causal role of the gut microbiota in the development and maintenance of alcohol addiction [2, 36]:

1) **Increased intestinal permeability:** An increase in intestinal permeability, also known as "intestinal hyperpermeability", corresponds to a functional and structural alteration of the intestinal barrier facilitating the uncontrolled passage of micro-organisms and microbial products from the intestinal lumen into the bloodstream [2]. This 'leakage' of luminal contents to the systemic level triggers immune activation resulting in increased production of pro-inflammatory cytokines and release of opioidergic mediators which play a central role in the brain's reward circuits involved in addiction [37]. Chronic alcohol consumption and the associated dysbiosis expose the intestinal barrier to pro-inflammatory substances (ethanol, acetaldehyde, LPS, bacterial peptides) which alter the assembly of intercellular tight junctions and the production of mucus, ultimately leading to hyperpermeability and its neuroinflammatory consequences [38].
2) **Production of psychotropic metabolites:** The intestinal microbiota produces a large number of metabolites from the fermentation of food substrates, some of which can cross the blood-brain barrier and exert psychoactive effects directly on the brain [39]. Translational studies in animals and humans have shown that chronic alcoholisation modifies the production of these metabolites both qualitatively and quantitatively, potentially contributing to the addictive effects of alcohol [36]. The compounds most commonly implicated are short-chain fatty acids (propionate, butyrate), some bile acids and biogenic amines such as tetrahydroisoquinolines [40, 41]. Their circulating levels are increased in alcoholic patients [36].
3) **Alteration of intestinal neurotransmitters:** Serotonin and dopamine are essential neurotransmitters involved in the brain's reward circuit. Stimulation of this circuit, particularly by addictive substances such as alcohol, leads to addictive behaviour by provoking feelings of well-being and pleasure [42]. The intestinal microbiota modulates serotonin and dopamine levels (see intestine-brain axis). Thus, alcohol-related dysbiosis leads to an overall drop in these bacterial metabolites and a reduction in serotonin/dopamine. As a result, the drop in serotonin and dopamine in the brain due to disturbances in the microbiota is thought to encourage alcohol consumption to over-stimulate the reward circuit. A vicious circle is created, leading to a reinforcement of addictive behaviour.
4) **Neuroinflammation:** The increased release of immune mediators, linked to intestinal hyperpermeability and the production of microbial metabolites, has the capacity to activate brain microglial cells, increase cerebral production of pro-inflammatory cytokines and thus promote the appearance of a central neuroinflammatory state, observed almost systematically in animal models of addiction [43]. Neuroinflammation modulates addiction circuits by increasing oxidative stress, glutamatergic excitotoxicity and reducing synaptic plasticity, leading to a progressive and persistent loss of behavioural control, increased impulsivity and anxiety, and increased craving [43, 44].

Although it is still difficult to establish whether intestinal dysbiosis is a cause or a consequence of alcohol addiction, it is currently accepted that dysbiosis plays a part in maintaining this dependence. In fact, studies conducted at the Catholic University of Louvain and Cliniques Universitaires Saint-Luc have shown that there is a link between intestinal dysbiosis and the severity of alcohol dependence. These studies involved alcohol-dependent patients hospitalised for a three-week withdrawal programme. Patients with intestinal dysbiosis had higher scores for depression, anxiety and craving for alcohol than patients without intestinal alterations, particularly at the end of withdrawal [2, 3].

These results suggest an important link between the gut and the brain in alcohol dependence, and suggest that alterations in the gut microbiota may be associated with a higher risk of relapse after alcohol withdrawal.

Therapeutic Perspectives

The pivotal role of the gut microbiota in addiction opens the way to new therapeutic approaches based on manipulation of the microbiota [4, 38, 45]:

- **Probiotics**: The administration of bacterial strains with beneficial properties (Lactobacilli, Bifidobacteria) capable of restoring the balance of the microbiota.

- **Prebiotics**: The administration of fibres and oligosaccharides that selectively stimulate the growth of endogenous beneficial strains.
- **Faecal transplantation**: Involves the introduction of a healthy microbiota taken from a donor and administered via the digestive or naso-intestinal tract.
- **Antibiotics**: Used as targeted treatments to eradicate bacteria identified as factors in dysbiosis/neuroinflammation.
- **Bacteriophages**: Viruses specific to a bacterial species, capable of regulating the composition of the microbiota in a targeted manner.

Initial clinical trials evaluating these approaches in alcohol-dependent patients have reported promising results in terms of reducing alcohol consumption and the severity of withdrawal [4, 46]. However, further studies are needed before large-scale application can be envisaged.

CONCLUSION

In conclusion, a growing body of converging evidence in humans and animals points to the gut microbiota as a key player in the development of alcohol addiction. Alterations in the composition and functionality of this microbiota are thought to play an active role in the addictive effects of alcohol via complex mechanisms involving intestinal permeability, psychoactive bacterial metabolites and neuroinflammatory phenomena. Manipulation of the microbiota using probiotics, prebiotics or faecal transplants therefore appears to be a promising therapeutic approach in the treatment of alcohol-dependent patients, which deserves to be explored further through in-depth studies.

Declaration of Conflict of Interest: The author declares no conflict of interest.

REFERENCES

1. World Health Organization. (2018). Global status report on alcohol and health 2018. Geneva: World Health Organization.
2. Leclercq, S., Matamoros, S., Cani, P. D., Neyrinck, A. M., Jamar, F., Stärkel, P., ... & Delzenne, N. M. (2014). Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. *Proceedings of the National Academy of Sciences*, *111*(42), E4485-E4493.
3. Quoilin, C., Amadieu, C., Fievez, F., Delzenne, N. M., de Timary, P., Duque, J., & Leclercq, S. (2023). Exploring the links between gut microbiota and excitatory and inhibitory brain processes in alcohol use disorder: a TMS study. *Neuropharmacology*, *225*, 109384.
4. Wang, S. C., Chen, Y. C., Chen, S. J., Lee, C. H., & Cheng, C. M. (2020). Alcohol addiction, gut microbiota, and alcoholism treatment: A review. *International journal of molecular sciences*, *21*(17), 6413.
5. Landman, C., & Quévrain, E. (2015). Gut microbiota: Description, role and pathophysiologic implications. *La Revue de medecine interne*, *37*(6), 418-423.
6. Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., & Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature*, *489*(7415), 220-230.
7. Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., ... & Wang, J. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *nature*, *464*(7285), 59-65.
8. Sender, R., Fuchs, S., & Milo, R. (2016). Revised estimates for the number of human and bacteria cells in the body. *PLoS biology*, *14*(8), e1002533.
9. Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., ... & Relman, D. A. (2005). Diversity of the human intestinal microbial flora. *science*, *308*(5728), 1635-1638.
10. Hou, K., Wu, Z. X., Chen, X. Y., Wang, J. Q., Zhang, D., Xiao, C., ... & Chen, Z. S. (2022). Microbiota in health and diseases. *Signal transduction and targeted therapy*, *7*(1), 1-28.
11. Ley, R. E., Peterson, D. A., & Gordon, J. I. (2006). Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*, *124*(4), 837-848.
12. Callaway, E. (2019). C-section babies are missing key microbes. *Nature*. Doi: 10.1038/d41586-019-02807-x.
13. Bäckhed, F., Roswall, J., Peng, Y., Feng, Q., Jia, H., Kovatcheva-Datchary, P., ... & Wang, J. (2015). Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell host & microbe*, *17*(5), 690-703.
14. Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., ... & Gordon, J. I. (2012). Human gut microbiome viewed across age and geography. *nature*, *486*(7402), 222-227.
15. Ragonnaud, E., & Biragyn, A. (2021). Gut microbiota as the key controllers of "healthy" aging of elderly people. *Immunity & Ageing*, *18*(1), 1-11.
16. Levy, M., Kolodziejczyk, A. A., Thaiss, C. A., & Elinav, E. (2017). Dysbiosis and the immune system. *Nature Reviews Immunology*, *17*(4), 219-232.
17. Jandhyala SM, Talukdar R, Subramanyam C, et al. Role of the normal gut microbiota. World J Gastroenterol. 2015 Aug 7;21(29):8787-803.
18. Carding, S., Verbeke, K., Vipond, D. T., Corfe, B. M., & Owen, L. J. (2015). Dysbiosis of the gut microbiota in disease. *Microbial ecology in health and disease*, *26*(1), 26191.
19. Koh, A., De Vadder, F., Kovatcheva-Datchary, P., & Bäckhed, F. (2016). From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell*, *165*(6), 1332-1345.
20. Kelly, C. J., Zheng, L., Campbell, E. L., Saeedi, B., Scholz, C. C., Bayless, A. J., ... & Colgan, S. P. (2015). Crosstalk between microbiota-derived

short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. *Cell host & microbe*, *17*(5), 662-671.
21. Fung, T. C., Olson, C. A., & Hsiao, E. Y. (2017). Interactions between the microbiota, immune and nervous systems in health and disease. *Nature neuroscience*, *20*(2), 145-155.
22. Mayer, E. A. (2011). Gut feelings: the emerging biology of gut–brain communication. *Nature Reviews Neuroscience*, *12*(8), 453-466.
23. Socała, K., Doboszewska, U., Szopa, A., Serefko, A., Włodarczyk, M., Zielińska, A., ... & Wlaź, P. (2021). The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. *Pharmacological Research*, *172*, 105840.
24. Wu, W., Kong, Q., Tian, P., Zhai, Q., Wang, G., Liu, X., ... & Chen, W. (2020). Targeting gut microbiota dysbiosis: Potential intervention strategies for neurological disorders. *Engineering*, *6*(4), 415-423.
25. Kelly, J. R., Kennedy, P. J., Cryan, J. F., Dinan, T. G., Clarke, G., & Hyland, N. P. (2015). Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Frontiers in cellular neuroscience*, *9*, 166028.
26. Maiuolo, J., Gliozzi, M., Musolino, V., Carresi, C., Scarano, F., Nucera, S., ... & Mollace, V. (2021). The contribution of gut microbiota–brain axis in the development of brain disorders. *Frontiers in neuroscience*, *15*, 616883.
27. Qian, X. H., Song, X. X., Liu, X. L., & Tang, H. D. (2021). Inflammatory pathways in Alzheimer's disease mediated by gut microbiota. *Ageing research reviews*, *68*, 101317.
28. Yan, A. W., E. Fouts, D., Brandl, J., Stärkel, P., Torralba, M., Schott, E., ... & Schnabl, B. (2011). Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology*, *53*(1), 96-105.
29. Rogers, G. B., Keating, D. J., Young, R. L., Wong, M. L., Licinio, J., & Wesselingh, S. (2016). From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Molecular psychiatry*, *21*(6), 738-748.
30. Chen, P., Torralba, M., Tan, J., Embree, M., Zengler, K., Stärkel, P., ... & Schnabl, B. (2015). Supplementation of saturated long-chain fatty acids maintains intestinal eubiosis and reduces ethanol-induced liver injury in mice. *Gastroenterology*, *148*(1), 203-214.
31. Mutlu, E. A., Gillevet, P. M., Rangwala, H., Sikaroodi, M., Naqvi, A., Engen, P. A., ... & Keshavarzian, A. (2012). Colonic microbiome is altered in alcoholism. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *302*(9), G966-G978.
32. Maslennikov, R., Poluektova, E., Zolnikova, O., Sedova, A., Kurbatova, A., Shulpekova, Y., ... & Ivashkin, V. (2023). Gut Microbiota and Bacterial Translocation in the Pathogenesis of Liver Fibrosis. *International Journal of Molecular Sciences*, *24*(22), 16502.
33. Wang, C., Yan, J., Du, K., Liu, S., Wang, J., Wang, Q., ... & Yang, F. (2023). Intestinal microbiome dysbiosis in alcohol-dependent patients and its effect on rat behaviors. *Mbio*, *14*(6), e02392-23.
34. Engen, P. A., Green, S. J., Voigt, R. M., Forsyth, C. B., & Keshavarzian, A. (2015). The gastrointestinal microbiome: alcohol effects on the composition of intestinal microbiota. *Alcohol research: current reviews*, *37*(2), 223-236.
35. Inserm Alcohol and Health. Available at: https://www.inserm.fr/thematiques/neurosciences-sciences-cognitives-neurologiepsychiatrie/dossiers-d-information/alcool-et-sante
36. Gorky, J., & Schwaber, J. (2022). The role of gut-brain axis in alcohol use disorders: novel perspectives on neuroinflammation and neurotransmission. *Alcohol Alcohol*, *57*(2), 151-158.
37. Koob, G. F., Buck, C. L., Cohen, A., Edwards, S., Park, P. E., Schlosburg, J. E., ... & George, O. (2014). Addiction as a stress surfeit disorder. *Neuropharmacology*, *76*, 370-382.
38. Bull-Otterson, L., Feng, W., Kirpich, I., Wang, Y., Qin, X., Liu, Y., ... & Barve, S. (2013). Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of Lactobacillus rhamnosus GG treatment. *PloS one*, *8*(1), e53028.
39. Rook, G. A., Lowry, C. A., & Raison, C. L. (2013). Microbial 'Old Friends', immunoregulation and stress resilience. *Evolution, medicine, and public health*, *2013*(1), 46-64.
40. Litwinowicz, K., & Gamian, A. (2023). Microbiome alterations in alcohol use disorder and alcoholic liver disease. *International Journal of Molecular Sciences*, *24*(3), 2461.
41. Quertemont, E. (2004). Genetic polymorphism in ethanol metabolism: acetaldehyde contribution to alcohol abuse and alcoholism. *Molecular psychiatry*, *9*(6), 570-581.
42. Clarke, G., Grenham, S., Scully, P., Fitzgerald, P., Moloney, R. D., Shanahan, F., ... & Cryan, J. (2013). The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Molecular psychiatry*, *18*(6), 666-673.
43. Crews, F. T., Lawrimore, C. J., Walter, T. J., & Coleman Jr, L. G. (2017). The role of neuroimmune signaling in alcoholism. *Neuropharmacology*, *122*, 56-73.
44. Mayfield, J., Ferguson, L., & Harris, R. A. (2013). Neuroimmune signaling: a key component of alcohol abuse. *Current opinion in neurobiology*, *23*(4), 513-520.
45. Zhang, B., Zhang, R., Deng, H., Cui, P., Li, C., Yang, F., & Leong Bin Abdullah, M. F. I. (2023). Research protocol of the efficacy of probiotics for the treatment of alcohol use disorder among adult males: A comparison with placebo and acceptance and commitment therapy in a randomized controlled trial. *PloS one*, *18*(12), e0294768.