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BIONE
E-ZINE OF BIOLOGICAL SCIENCES
ISSN: 2456-7264 | Issue – 10 | Published On 02/05/2019

Alcohol and gut microbiota in gut-brain and gut-liver axis

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Recent advances in the gut microbial research have shed the light on the importance of gut microbiota and its contribution in maintaining our health. The gut microbiota maintain a homeostasis in the body and thus contribute to metabolism and immunity development, and any perturbation in the gut microbial homeostasis leads to diseases. Involvement of gut microbiota in the disease development is not only restricted to localised effects as in inflammatory bowel disease but it can also effect at distant sites such as liver, heart, brain and the hematopoietic system.

The intestinal barrier is an integral part of the gastrointestinal tract which comprises several physical and immunological layers. Specifically, the intestinal barrier (Figure 1) comprises of i) Mucus layer that contains commensal microbiota, secretory immunoglobulin A (IgA) and anti-microbial peptides, ii) The epithelial intestinal layer which acts as a physical barrier that contains tight junctional complexes, adherens junctions and desmosomes between intestinal epithelial cells (IECs), and finally iii) Lamina propria with its resident population of innate and adaptive immune cells such as T and B cells, macrophages, dendritic cells of Peyer's patches and mesenteric lymph nodes that make up the intestinal immune barrier[1]. Physical intestinal barrier prohibits bacterial translocation from the lumen and allows selective absorption of critical nutrients required by the host, and any perturbation to this tightly regulated intestinal barrier could lead to a leaky gut and allow bacterial endotoxins to penetrate the mucosa and enter the systemic circulation. Alcohol consumption is reported to disrupt the

functional and structural integrity of IECs contributing to increased gut leakiness by a variety of mechanisms[2,3]. After consumption, alcohol is absorbed by different cells in the mouth, stomach and intestine and only a small amount is metabolized in the cells. However, a majority of alcohol that is consumed passes directly into the blood stream due to its hydrophobicity. Alcohol travels through blood to the liver where it undergoes metabolism. A number of enzymes are involved in alcohol metabolism, the most well-known are Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the liver[4]. Initially, ADH converts alcohol into acetaldehyde which is a highly toxic carcinogen. Acetaldehyde promotes alcohol dependence and is found in all the regions of the brain following alcohol consumption. Acetaldehyde is highly pro-inflammatory; it activates complement cascade recruiting neutrophils and eliciting production of reactive oxygen species (ROS)[5]. Though highly toxic, acetaldehyde is quickly metabolized by ALDH to form acetate, which is then finally converted to carbon dioxide and water that can be removed from the body easily.

Alcohol and the intestinal microbiota

Alcohol is known to alter the intestinal microbiome by altering the intestinal microenvironment that favours the growth of pathogenic bacteria over that of non-pathogenic commensal bacteria. An alteration in function and composition of colonic microbiome was reported in alcoholic patients with reduction in *Bacteroidetes* and increase in *Proteobacteria*[6]. Chen et al.[7] also reported an increase in *Proteobacteria* along with increased prevalence of *Fusobacteria* in hepatitis B virus (HBV) and alcohol related cirrhotic patients. Alcohol mediated over-growth of intestinal bacteria and dysbiosis was reported in conventional mice with an increased prevalence of Enterobacteriaceae[8]. Studies on mice reported relative abundance of *Bacteroidetes* and *Verrucomicrobia* in alcohol-fed mice compared to control mice with relative predominance of *Firmicutes*[9]. Over-growth of *Akkermansia muciniphila*, a mucin degrader, was also reported in alcohol-fed mice[10].

Increase in ROS following ethanol exposure contributes to disruption in intestinal homeostasis and hypothalamic homeostasis by increasing the oxidative stress through nitric oxide (NO). At the normal level, NO is involved in maintaining normal intestinal

barrier function[11]. However, when NO is in excess after chronic alcohol consumption, it results into barrier disruption and increased gut leakiness[12]. Thus destruction of the barrier integrity of the intestinal epithelium caused by alcohol abuse could allow translocation both bacteria and their products including lipopolysaccharides (LPS) from the gut to the circulation[13] resulting in systematic inflammation. Alcohol also has a stimulatory effect on neuroendocrine hormones such as Cortico-trophin releasing hormone (CRH), which can lead to an increase in gut permeability[14]. Circulating LPS was reported to increase the pro-inflammatory cytokines, TNF-α in the brain, liver and serum[15] while anti-inflammatory cytokines IL-10 was reported to decrease in both brain and intestinal tissues[16]. Thus alcohol consumption causes a direct effect on the brain and the intestine by inducing neuro-inflammation and intestinal inflammation, respectively. Interestingly, germ-free mice showed reduced liver pathology after alcohol administration compared to that in conventional mice which showed the involvement of gut microbiota in the development of alcoholic liver diseases.

Alcohol and the gut brain axis

Sudo et al.[17] reported for the first time the link between the intestinal microbiota and the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is extremely important in generating a proper stress response and is slowly developed through adolescence. Germ-free mice do not have properly develop HPA axis. Alcohol has been shown to activate the HPA axis leading to an increase in corticosteron in the circulatione in mice and rats following a single binge[18]. Many research groups have shown profound effects of heavy alcohol drinking from young age on the brain and development of depressive like behaviour[19,20], while altered bacterial populations in the gut appears to have numerous negative effects on the CNS[21,22]. On the contrary, probiotics treatment can reduce the psychological stress induced due to alcoholism[23]. Intestinal microbes can directly interact with the CNS through vagus nerve stimulation and enteric nervous system[24]. Studies have reported that the exposure of certain gram negative bacteria that induce inflammation can lead to changes in the neuronal activity in the hypothalamus and central brain regions[25]. Other than bacteria, bacterial metabolites

can also influence inflammation and neuronal signalling in the CNS[26]. The gut bacteria has the ability to alter the neurochemical signals such as brain-derived neurotrophic factors (BDNF), gamma-aminobutyric acid (GABA) and serotonin. A reduced expression of BDNF proteins was reported in mice with anxiety like behaviour[27]. Deregulation of GABA signalling was reported during anxiety and depression like behaviour[28]. Gut is one of the largest producers of serotonin in the body and intestinal dysbiosis can lead to altered serotonin expression which can effect neuronal signalling of the brain[29].

Alcohol and Gut-liver axis

The gut liver axis is a major pathway for development and progression of alcoholic liver diseases. Liver plays an essential role in modulation of gut microbiota and its effect through multiple functions, including bile acid production and enterohepatic circulation as well as exposure to gut bacterial end-products along with nutrients via the portal vein[30]. Liver does not only receive nutrient-rich blood from the intestine, but also acts as the first target for the intestinal microbiota through microbe-associated molecular patterns (MAMPs) which can elicit inflammatory responses via pattern recognition receptors (PRPs) and microbial metabolites. The multilayer intestinal barrier protects the liver from exposure to pro-inflammatory MAMPs. However, alteration in the gut bacteria and failing gut barrier in chronic liver diseases (CLD) contribute to chronic inflammation and progression of liver diseases[31,32] and thereby increase the risk of hepatocellular carcinoma (HCC). Liver produces bile acids which is released into the duodenum in conjugated form, where they undergo microbial modification and participate in the enterohepatic cycling through the farnesoid X receptor (FXR)-fibroblast growth factor 19 (FGF-19) axis that can modulate the gut barrier and an integral part of the gut-liver axis.

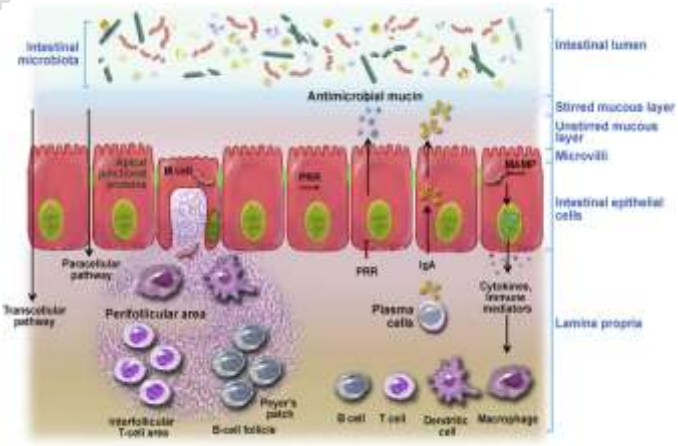

Figure 1: Intestinal barrier as modulator of intestinal homeostasis. Intestinal barrier is equipped with both physical and immunological barrier system. (Figure is adapted from Vanner *et al*., 2016)

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