Gut permeability alterations mediated by bacteria and links to alcohol dependence...

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The study entitled “ Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity” by Leclercq et al., (Proceedings of the National Academy of Sciences 111. 42 (2014): E4485-E4493) explores the possibilities of links between alterations in gut permeability, composition of gut-microbiota, as well as the activity of the gut metabolites and the increased depression, anxiety, and alcohol craving in alcohol-dependent subjects. Thus, the study aims to establish an association between gut dysfunction and the psychological symptoms resulting from alcohol dependence. In addition, reversibility of behavioral as well as biological parameters, after a short term alcohol detoxification was determined. There is a correlation between altered gut microbiota composition and psychiatric disorders. The correlation suggests that there is a gut-to-brain interaction that exists in the development of dependence to alcohol. Individuals who are alcohol-dependent (AD) and are actively involved in drinking alcohol also show a raised level of intestinal permeability (IP) as well as enhanced levels of gut-derived bacterial products such as peptidoglycans and lipopolysaccharides in the plasma. The bacterial products have also been shown to activate specific inflammatory pathways, which are recoverable after a short-term alcohol abstinence. These facts are the major reasons why the researchers were looking for the relationship between gut bacteria and alcohol intake behavior. Lack of intestinal microbiota balance or dysbiosis may contribute a number of diseases such as type 2 diabetes, obesity, allergy, and inflammatory bowel disease. Gut bacteria have also been shown to influence the functioning of the brain and behavior suggesting the function bacteria in the gut in the onset psychiatric

disorder. The study was conducted with an aim of determining the association between gut permeability and severity psychological symptoms that develop in AD individuals. The study also aimed at determining the association of gut permeability and severity of psychological symptoms that develop in AD individuals. The composition as well as activity of the microbiota from the gut were also assessed and their relation to gut permeability was tested. Finally, the study tested whether the altered microbiota composition, gut permeability, and microbiota metabolome are reversible after abstaining from alcohol for 3 weeks.

The study used a group of subjects who were AD and presented with alcohol dependence symptoms. The subjects were evaluated clinically by a psychiatrist and incorporated into the study. The subjects were admitted to the gastroenterology ward where they were taken through a 3-wk rehabilitation and detoxification program. In a preliminary study, a total of 60 AD subjects who were tested for psychological symptoms and intestinal permeability on the day (T1) after admission. From the 60 subjects, 44 of them did not take alcohol until the last day and were also tested at the final day of detoxification (T2). These subjects were then divided into low IP and high IP groups. Thirteen subjects consisting of eight men and five women were also evaluated for the composition of gut-microbiota as well as microbiota functionality at T1 and T2. Comparison was done on the basis of psychological dimensions, intestinal permeability, and composition and functionality of gut-microbiota.

Measurement of intestinal permeability was done through the use of 51Cr-EDTA method. The results obtained revealed that at T1, 43% of the subjects

showed high levels of gut permeability, and the rest (57%) showed normal gut permeability when compared with the control group. The subjects were then divided into two groups, high IP and low IP according to the deviance criterion using a cutting point of 1. 65 Standard Deviations of the control group's mean.

The measured gut permeability of the high IP AD subjects at T2 showed a significant decrease, with the mean of this group being equal to the mean IP recorded at T1 for the low IP AD subjects and the control group. Since only the AD individuals who showed a high level of IP had alteration of the microbiota in the gut in comparison with the control group, the involvement of some bacteria in regulating the gut-barrier function was tested. The correlation between IP and gut bacteria at T1 was negative indicating that those who had a high IP had a reduced number of bacteria in the gut. A negative correlation was also revealed in some types of bacteria such as those belonging to the Ruminococcaceae family. The reduced number of bacteria in the high IP subjects supports the idea that the quantity of microbiota in the gut may be useful in the gut-barrier function. The assessment of psychological status in AD subjects revealed a high level of all the psychological scores (alcohol craving, anxiety, and depression) in all AD subjects except the control subjects. By the end of the detoxification program, the anxiety and depression scores in AD subjects who had a low IP was similar to that of the control subjects. The subjects with high IP did not show a reduction in the anxiety, depression, as well as craving scores.

The results obtained in the study clearly indicate that dysbiosis is highly associated with alteration of gut-barrier in AD subjects with a high level of

intestinal permeability. The alterations in the quantity of the microbiota in the gut is thus associated with an increase in the level of intestinal permeability as well as an increase in pro-inflammatory cytokines in the plasma.

Psychological symptoms were not recovered in an even manner among the tested AD subjects. The subjects who had a low IP recovered almost fully from the symptoms while the high IP subjects did not. This may be the main contributor to negative reinforcement process, which is related to the increased chances of relapse after the detoxification process is complete. Low IP subjects recovered completely from anxiety and depression indicating that the group did not experience severe dependence to alcohol. The lack of recovery from psychological symptoms by the subjects who had a high level of intestinal permeability implies that permeability of the gut, to a greater extent, dependent on the psychological state of the subject at the end of detoxification program. Increase in the content of the bacteria in the Ruminococcaceae family is an indication that this bacterial family has a beneficial impact on the barrier functions of the gut. The increase in the number of these bacteria may have also been involved in the recovery IP by the end of the detoxification period. The strong negative correlation between IP and the amount of the bacteria in the gut supports the idea of the bacteria working as barriers. These results have shown that an increase in gut permeability has an association with dysbiosis in AD subjects. The reported observations are also in agreement with the role played by gut microbes as protective agents. The protective role is achieved through the production of indolic compounds, as well as p-cresol on the gut barrier and inflammation.

The present study is pivotal and paves the way for avenues in several previously unexplored research in the understanding, management, treatment, and development of novel therapeutics for alcohol dependence. Future research studies should focus on

- Extending and establishing the associations identified in the present study into clear correlations such that AD could be studied from the perspective of gut flora.
- Provided the associations can be established as correlations, extend the research studies into larger cohorts to confirm the findings.
- Identify the specific bacterial strains involved in the gut permeability alterations in AD.
- Explore the bacteria, gut permeability and diet change (to affect changes to gut flora) as potential targets to develop therapeutic or other alternate treatments for AD.
- Determine the nature and extent of involvement of the metabolites produced by gut bacteria in the development of gut-barrier dysfunction in relation to inflammation.