124

Innate Gut Microbiota Is Required for the Acquisition of Ethanol Intake and Relapse Binge-Drinking by Wistar-Derived High Drinker Rats

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Several human studies report that alcohol exposure alters intestinal microbiome causing dysbiosis, and in animal models fecal transplants from alcoholics patients increase alcohol preference. There is, however, no evidence linking the innate gut microbiome of rats selectively bred as high drinkers to their elevated ethanol intake. This was investigated in the high-alcohol drinker Wistar-derived UChB rats. In initial studies, gut microbiota of male UChB rats was eliminated *prior to offering ethanol* by the daily administration of two or three antibiotics (ABX-1 = neomycin 250 mg/kg + polymyxin-B 9 mg/kg) or (ABX-2 = neomycin 250 mg/kg + polymyxin-B 9 mg/kg + metronidazole 50 mg/kg). Both ABX-1 and ABX-2 were administered by oral gavage for 7 consecutive days while ethanol solutions (10; 20 and 30%) or water were offered 24-hours *after* the last antibiotic dose.

Treatment with antibiotics ABX-1 or ABX-2 markedly inhibited (80% $p < 0.0001$) voluntary ethanol intake versus vehicle (water), inhibition that remained constant for at least seven days. Neither total fluid intake nor weight gain was affected by antibiotic treatment. Subsequently the role of gut microbiota on alcohol relapse binge-like intake was studied in rats that were offered 33 days of continuous free-choice ethanol access (reaching intakes of 10 g ethanol/kg/day), followed by a 14-day ethanol deprivation period prior to ethanol re-access. Again, to avoid possible ethanol-induced pharmacodynamics/kinetic effects, the antibiotics (ABX-1 or ABX-2) or vehicle (water) were not administered while animals were ingesting ethanol but *administered daily during the ethanol deprivation period* (on the last 7 deprivation days). Upon ethanol re-access control (vehicle) rats showed the known binge-like ethanol intake (2 g ethanol/kg/60 minutes, reaching blood ethanol of 125 mg/dl), intake that was inhibited by 50% and 55% ($p < 0.001$) by ABX-1 and ABX-2 respectively. Treatment with ABX-1 or ABX-2 during de last seven deprivation days did not affect total fluid intake or weight gain. Overall, this study suggests that innate gut microbiota plays an important role in the susceptibility of UChB rats to ingest large amounts of alcohol both on the acquisition/maintenance and relapse. Whether in humans innate microbiota may relate to the development of alcohol-use-disorders is not known. Fondecyt #1180042; #1190562; #1200287.