Metabolomic Core, and [4]Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester MN 55901, USA.

Abstract

Using acamprosate as a probe medication, we aim to discover serum biomarkers to predict antidipsotropic treatment outcome and to uncover metabolic pathways associated with the pharmacological effect of these medications in patients with alcohol use disorder. We analyzed serum samples from 84 alcohol dependent subjects collected at baseline (before treatment) and after 3 months of acamprosate treatment using an untargeted global metabolomics approach. Subjects were classified as responders if they maintained complete abstinence during the treatment period. Based on our findings, we performed functional studies in mice. At baseline, 48 metabolites were significantly different between response groups and 26 of these metabolites remained different after 3 months of acamprosate treatment. Comparing metabolites at the 3-month time point to baseline, responders showed significant changes in 100 metabolites whereas non-responders only showed changes in 16 metabolites. Five metabolites were similarly changed in both groups. Pathway analysis with 95 metabolites, which were uniquely changed in the responders, identified a significant enrichment in caffeine metabolism. Specifically, caffeine metabolites were increased at the 3-month time point in responders compared to non-responders. Animal studies showed that caffeine co-administration improves the pharmacological effect of acamprosate in reducing ethanol intake. We identified a panel of baseline metabolites that is associated with acamprosate treatment response. In addition, after 3 months of acamprosate treatment, we identified that caffeine metabolites are associated with acamprosate treatment response, indicating serum metabolite biomarkers will be useful for the personalized treatment in alcoholism.

PM308

A phase 3, multicenter randomized double blind placebo controlled study of the opioid receptor antagonist –Odelepran the treatment of alcohol addiction.

E. Krupitsky[1], E.Mukhametshina [2], M.Samsonov [2]

[1]. Department of Addictions, St.-Petersburg Bekhterev Research Psychoneurological Institute, Russia [2]. R - Pharm CJSC, Russia

Abstract

Educational Objectives: Odelepran is a new pan opioid receptor antagonist for the treatment of alcohol dependence. Odelepran demonstrates high in vitro binding affinity (K*i*) and antagonist potency (K*b*) at all 3 classic human opioid receptors (mu, kappa, and delta).

Odelepran has a potential to decrease the amount of alcohol drunk by a patient, as well as to block the effects of opiates, thus helping patients to abstain from using these potent substances of abuse. The preclinical research programme for peroral Odelepran formulation is completed by now, as are phase I and phase II clinical studies in patients with alcohol dependence.

Methods: This was multi-center randomized double blind placebo controlled phase III clinical studies for assessment of efficacy and safety of Odelepran with a 24-week treatment period. Patients (N = 644) were alcohol-dependent, treatment-seeking adults. Clinical trial was in Russia.

Inclusion criteria: patients with alcohol dependence of moderate severity (5–12 drinks/day). Primary endpoint: the mean number of drinks per drinking day. Medical Management on compliance issue only to reduce placebo effect.

Analysis for genotyping: the coding target preparation OPRM1 rs1799971.

To assess the efficacy we used psychometric scales: Retrospective analysis of alcohol consumption (TLFB), Assessment of the consequences of drinking (questionnaire DrInC-2R), Assessment of craving for alcohol (Obsessive-Compulsive Scale), Subjective assessment of the patient quality of life (SF-36).

Conclusions: in clinical trial was included 644 patients with alcohol-dependent (DSM-V/ISD-10): Female- 192 patients, Men-452 patients and a average age from 25–49.

Interim safety analysis showed no serious adverse effects, good tolerability and fewer drink per day compared with placebo. The final data will be presented in June 2016.

PM309

Methamphetamine induced changes of monoamine neurotransmission in 5-HT1B KO mice

Yuki Moriya[1], Yoko Hagino[1], Scott F Hall[2], René Hen[3], Kazutaka Ikeda[1], Yoshiyuki Kasahara[4], Ichiro Sora[5], George R. Uhl[6]

[1]Tokyo Metropolitan Institute of Medical Science, Japan, [2]Toledo Univ. Pharmacy and Pharmaceutical Sciences, USA, [3]Columbia University, USA, [4]Tohoku University, Japan, [5]Kobe University, Japan, [6]Molecular Neurobiology Branch NIDA-IRP, USA

Abstract

Objectives: Monoaminergic systems, including those that act via 5-HT1B receptors, may play key roles in regulating locomotor stimulation that follows acute and/or chronic methamphetamine (METH) administration. We have previously found that behavioral sensitization to METH (1mg/kg) was enhanced in homozygous 5-HT1B receptor knockout (5-HT_{1B}-/-) mice compared to wild-type (WT) mice, but was attenuated in heterozygous 5-HT1B receptor knockout (5-HT_{1B}+/-) mice compared to WT and 5-HT_{1B}-/- mice. We now report attempts to seek alterations in extracellular serotonin (5-HT_{ex}) levels following administration of METH that might correlate with levels of locomotor sensitization in WT and 5-HT_{1B} KO mice.

Methods: We used the *in vivo* microdialysis technique for the measurement of extracellular monoamine levels in awake WT, 5-HT_{1B}+/-, and 5-HT_{1B}-/- mice.

Results: *In vivo* microdialysis demonsrates that acute administration of METH (1 or 3mg/kg) increases extracellular dopamine (DA) levels in the caudate putamen (CPu) and nucleus accumbens (NAc) of wildtype and knockout mice. In the NAc, both 1 and 3 mg/kg METH doses induced larger DA increases in knockout than in WT mice. Basal NAc dialysate DA concentrations were also higher in knockouts than in WT mice, though we identified no differences in CPu. Nevertheless, in CPu the effect of METH was larger in 5-HT_{1B}-/- mice than in WT mice at the 3mg/kg, but not at 1mg/kg.

Conclusions: In comparing neurochemical differences in homozygous 5-HT_{1B} KO vs WT mice, we found that the increased locomotor sensitization in 5-HT_{1B}-/- mice is associated with greater effects of METH on extracellular DA and 5-HT levels. By contrast, in 5-HT_{1B} +/- mice the relative increases in 5-HT_{ex} are greater than those for DA compared to WT mice. Extracellular 5-HT levels may contribute to the differential effects of METH in heterozygous and homozygous 5-HT_{1B} knockout mice on locomotor activity.