Abstract

Objectives: Venlafaxine is metabolized by CYP2D6 to O-desmethylvenlafaxine (ODV) and by CYP3A4 to N-desmethylvenlafaxine (NDV). CYP2C19 is also involved in the formation of ODV. The PPIs omeprazole and pantoprazole inhibit CYP2C19 to a different extent. Aim of this study was to investigate the potential effects of both PPIs on serum levels of VEN and ODV.

Methods: From a therapeutic drug monitoring (TDM) database, serum concentrations of VEN, ODV and the active moiety (VEN + ODV), were analyzed. Data from 120 patients were available and split into three groups: patients without PPI [noPPI], with pantoprazole [PANTO] or with omeprazole [OMEP] (n=40 each). The ratio of (ODV/VEN) was calculated as a marker of the metabolizer status.

Results: Median test detected no differences regarding the median daily dosage of VEN between the three groups (p=0.995); the mean daily doses for VEN were 207.6mg/d, SD=79.96 in the control-group, 209.06mg/d, SD=78.24 for the pantoprazole group and 203.43mg/d, SD=91.41 for omeprazole group. Plasma concentrations for VEN + ODVEN in the PANTO group were significantly higher than in the control group (p=0.019 for Mann-Whitney U Test). Plasma concentrations for ODVEN and VEN + ODVEN in the OMEP group were significantly higher than in the control group (p=0.001 and p=0.017 for Mann-Whitney U Test)

Conclusion: Both, omeprazole and pantoprazole led to a varying extent in increases of the serum concentrations of the active moiety (sum of VEN+ODV). The increase is driven by significantly higher levels of ODV in the OMEP group. This might be due to distinct CYP2C19 blocking properties of both PPIs, hindering the 2C19 mediated metabolization of VEN to N-desmethylvenlafaxine (NDV).

PS213
Pharmacokinetics of mirtazapine and its hydroxylated metabolite in Japanese psychiatric patients treated with mirtazapine
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Abstract

Purpose: This study investigated the pharmacokinetics of mirtazapine (MIR) and its hydroxylated metabolite in Japanese psychiatric patients.

Patients and Methods: The subjects were 59 Japanese patients treated with racemic MIR. The steady-state plasma concentrations of MIR and N-desmethylmirtazapine (DMIR), 8-hydroxymirtazapine (8-OH-MIR) were measured using high performance liquid chromatography. CYP2D6 genotypes were determined by polymerase chain reaction. Three subjects whose plasma levels of MIR and DMIR were below the limit of detection were regarded as non-adherent and excluded. Multiple regression analysis (stepwise method) was performed to analyze the relationship between subject-independent variables (gender, age, smoking status and number of mutated CYP2D6 alleles) and subject-dependent variables such as plasma concentrations of MIR, DMIR, 8-OH-MIR (ng/ml/mg/kg; all corrected for dose and body weight) and 8-OH-MIR/MIR ratio.

Results: Multiple regression analysis revealed that smoking (p=0.016) and gender (p=0.041) had a significant impact on plasma concentrations of MIR. The final models were described by the following equations: Plasma concentration of MIR = 86.6 - 31.9 x smoking status (smoking=1, non-smoking=0) - 23.0 x gender (male=1, female=0) (R= 0.45, p=0.002, coefficient of determination (R²) =0.20). Smoking status was a significant factor correlated to plasma concentration of 8-OH-MIR (p=0.034). The final model was described by the following equation: Plasma concentration of 8-OH-MIR (corrected for dose and body weight) = 2.41 - 1.59 x smoking status (smoking=1, non-smoking=0) (R= 0.29, p=0.034, R²=0.08). There were no significant factors correlated to 8-OH-MIR/MIR ratio in the multiple regression analysis.

Conclusion: Gender and smoking polymorphism might affect pharmacokinetics of racemic MIR in Japanese patients.

PS214
Cerebral and peripheral Tryptophan / kynurenine pathway in the pathophysiology of stress-induced bio-behavioural abnormalities
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Abstract

KYN pathway (KP) is activated by pro-inflammatory cytokines and can produce pro-oxidative metabolites in the brain of depressed patients. Antidepressant treatment reverses oxidative stress in animal models, we can hypothesize that in an animal model of “chronic stress induced depression” in mice, we previously showed that TRP/KYN pathway activation produced glutamatergic and pro-oxidative metabolites (3-HK), suggesting that chronic stress accelerates glutamatergic excitotoxicity and oxidative stress. We show here that a chronic treatment with the IDO (indole dioxygenase) inhibitor 1-methyl-tryptophan (1MT) or antidepressant fluoxetine were able to reverse TRP/KYN abnormalities caused by chronic stress. These data suggest that TRP/KYN pathway would play a central role in the pathophysiology of stress-induced bio-behavioural abnormalities.

Methods: Mice were confronting the unpredictable chronic mild stress (UCMS) procedure and brain KP metabolites were analysed in relevant brain structures and in the periphery, in saline, 1-MT and fluoxetine treated animals.

Results: 1-MT and FLX reverse most of UCMS-induced behavioural abnormalities induced by UCMS and reverse various metabolic alterations of the KP (peripherally and centrally).

Conclusions: Our results show that inhibition of the KP by 1MT is as effective as fluoxetine as an antidepressant treatment in the UCMS mice. They show that inhibiting KP subsequently reduces the production of pro-oxidative /neurotoxic metabolic substrates in relevant structures. They suggest that KP would play a central role in the link between neuroinflammation and oxidative stress abnormalities in chronic stress induced mood disorders.

PS215
Microglial STAT3 regulates depressive-like behavior by modulating cytokine expression via neuro-glia communication
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Abstract

Microglia are commonly known as the resident immune cells and have emerged as key players for neuro-immune system. However, the underlying mechanisms of neuro-glia interaction are poorly understood. Here, we investigated how microglia affect neural functions and behavioral responses. To make concrete, we used microglia specific STAT3 knock-out (KO) mice via Cre-loxP recombination system. Primarily, we found that immobility time in forced swim test and tail suspension test were reduced not only in microglial STAT3 KO group but also in the groups exposed to acutely and chronically induced restraint stress. From cytokine profiling assays, we identified that level of M-CSF was increased in microglial STAT3 KO mice. To decipher the mechanisms, we employed in vitro co-culture system between BV2 cells and HT22 cells. Surprisingly, level of M-CSF mRNA was higher in HT22 cells cultured with STAT3 knocked-down BV2 cells. Likewise, secreted form of M-CSF was increased in the same co-cultured media. Moreover, M-CSF treatment on HT22 cells significantly induced phosphorylation of ERK1/2, Akt, GSK3β, which were known as signal mediators for synaptic activities and especially antidepressant pathways. Interestingly, we discovered the increased level of BDNF in HT22 cells and co-culture systems after M-CSF treatment. The same results were confirmed in microglial STAT3 KO mice. Concerned with synaptic functions, mEPSC frequency of medial prefrontal cortex was increased in the microglial STAT3 KO mice and M-CSF treatment group. Our findings open the possibility that microglial STAT3 modulates neuronal cytokine expression and synaptic activity, and consequently regulates depression and stress-related behaviors.

PS216

Preclinical and clinical assessment of tryptophan catabolites (TRYCATS) as a measure of neuroinflammation and utility in compound screening.

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Abstract

Numerous studies measuring pro-inflammatory cytokines in blood demonstrate that a subpopulation of psychiatric patients exhibit inflammation. In post-mortem and imaging studies, neuroinflammation was indicated by the presence of activated microglia. Since tryptophan catabolism increases in activated microglia, tryptophan catabolites (TRYCATs) are possibly novel biomarkers of neuroinflammation-induced psychiatric symptoms.

Specific objectives: A) Assess TRYCATs in animal models of neuroinflammation to determine utility as an endpoint for therapeutic intervention. B) Assess TRYCAT levels from psychiatric patients and controls as a potential clinical biomarker for patient stratification.

Methods Used: LPS model: LPS was injected i.c.v. to mice, and brains were collected 24 hours later. Chronic Social Defeat model: Mice were subjected to chronic social defeat in a standard paradigm. Brains were collected on the final day of testing. Clinical samples were obtained from the Universitätsklinikum Ulm, Germany. TRYCATs in mouse brain tissue homogenates/plasma and human CSF/plasma were analysed using liquid chromatography-tandem mass spectrometry.

Results: LPS model: A robust increase in all TRYCATS from brain homogenates was observed in all LPS treated animals. Chronic social defeat model: No change in TRYCATs was observed in mice subjected to chronic stress. However, a significant proportion of microglia became activated following chronic social defeat. Inhibition of the IDO1 enzyme, which catalyses the first step in the TRYCAT pathway, reversed TRYCAT induction in the LPS model, as well as behavioral alterations in chronic social defeat. Results from the clinical samples indicate that patients exhibit an altered TRYCAT profile, and that CSF and plasma TRYCATs appear to be independently regulated.

Conclusion: TRYCAT levels provide a useful tool for preclinical models of neuroinflammation and treatment. A first study of TRYCATs in a patient population suggests potential use as a clinical biomarker.

Reference

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PS217

Persistent glucocorticoid receptor activation reduces M2-like microglia phenotypes via TNF-α pathway

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Abstract

Persistent glucocorticoids (GCs) exposure in chronic stressful stimuli has deleterious effects on the function of neuron and microglia, leading to major depression. In the previous study, we reported that the dysregulation of microglia functional phenotype in chronic stress mice was associated with stress vulnerability and depression relapse. However, the underlying mechanism of glucocorticoid on microglia functional phenotype was not elucidated until now. In this study, we investigated that 72h of dexamethasone (DEX) treatment reduced fractalkine receptor (CX3CR1) and CD200 receptor (CD200R) in primary cultured microglia while 24h of DEX did not. In addition, the effect was abolished by RU386 (Gc antagonist) co-treatment, suggesting that glucocorticoid receptor (GR) mediates the dexamethasone effect on CX3CR1 reduction in microglia. Interestingly, we found that 72h of DEX treatment increased TNF-α and IL-6 secretion in microglia while 24h of DEX treatment did not. TNF-α neutralizing antibody co-treatment with DEX also could prevent microglia from reducing CX3CR1 expression. Overall, our results suggest that chronic glucocorticoid exposure reduced M2-like phenotype of microglia (CX3CR1 and CD200R) via TNF-α elevation, which may be involved in stress vulnerability and depression.

Key words: Microglia, Depression, CX3CR1, TNF-α, Glucocorticoid

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