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Neurokinin-1 Receptors in the Nucleus Accumbens Shell Mediate Sensitivity to Social Defeat Stress

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Background: Chronic social defeat stress (SDS) is a widely used preclinical model of depression. In this procedure, mice are exposed to a brief physical defeat by a larger, aggressive mouse for 10 consecutive days. Aggressor mice and defeated mice are then housed in the same cage, separated by a perforated divider, until the physical defeat session on the following day. Exposure to SDS induces depressive-like phenotypes in mice including anhedonia, social withdrawal, and increased drug and alcohol consumption. In our prior work, we have found that expression of the neurokinin-1 receptor (NK1R) is increased in the nucleus accumbens (NAC) of mice that are sensitive to this stressor. The NK1R is the endogenous receptor for the neuropeptide substance P, and plays a prominent role in stress, anxiety, and addiction.

Methods: In the present study, we used genetic, pharmacological, and viral vector strategies to demonstrate a functional role of the NK1R in the NAC shell in sensitivity to SDS.

Results: First, we exposed NK1R -/-, which have a genetic deletion of this receptor, to the SDS procedure. Surprisingly, we found no effect of this genetic manipulation on sensitivity to SDS. We hypothesized that this was due to developmental compensatory adaptations in the neurokinin systems in these mice. To inhibit the NK1R without affecting developmental adaptations, we delivered the NK1R antagonist L703606 prior to each physical defeat and found that this treatment was able to decrease the sensitivity to SDS exposure, providing protection from the social withdrawal inducing effects of this stressor. Conversely, we then overexpressed the NK1R in the NAC shell using viral vector strategies and found that this increased the sensitivity to SDS.

Conclusions: Together, these experiments provide evidence for a functional role of the NK1R in the NAC shell in the sensitivity to SDS.

Keywords: Depression, Social Defeat Stress, Neurokinin, Substance P, Neuropeptides

Disclosure: Nothing to disclose.

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Quantification of Antidepressant and Antipsychotic Exposure Increase Caused by CYP2C19 and CYP2D6 Intermediate and Poor Metabolizer Status

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Background: Most of the psychiatric drugs are metabolized by CYP2C19 and CYP2D6 enzymes. Both CYP2D6 and CYP2C19 genes are polymorphic and metabolic capacity of the enzymes is genotype-determined. Homozygous Null allele carriers do not possess active enzyme, and they are referred to as CYP2C19 or CYP2D6 poor metabolizers (PM). Certain genotypes do not abolish the enzyme completely, but they do cause a drastic reduction of metabolic capacity and carriers of such genotypes are referred to as intermediate metabolizers (IM). It is known that CYP2C19 and CYP2D6 PM and IM status cause an increase in exposure of certain antidepressants and antipsychotics; however, due to small sample sizes of the previously published studies, the magnitude of this effect still cannot be estimated with sufficient precision. Therefore, the aim of this meta-analysis was to pool all these studies and estimate the magnitude of drug exposure increase caused by CYP2C19 and CYP2D6 PM and IM status, compared with normal metabolizers (NM).

Methods: The inclusion of the drugs used for the literature survey for meta-analysis was based on the list of new-generation antidepressants and antipsychotics found on consensus guidelines for therapeutic drug monitoring. Initially, the studies were screened for inclusion by the PubMed search 'DrugName' AND (CYP2C19 OR CYP2D6) for all listed drugs. The studies were included in the meta-analysis if (1) the patients were appropriately genotyped for CYP2C19 or CYP2D6; (2) adequate sorting of patients into NM, IM, and PM was possible; (3) the study included at least three patients per subgroup; and (4) drug exposure was measured in a representative way as (a) dose-harmonized area under plasma level (time) curve, (b) dose-harmonized steady-state plasma levels, or (c) apparent total clearance of the drug from plasma after oral administration (CL/F, reciprocal value represented the drug exposure). Meta-analysis for a specific drug was performed if five or more studies met the inclusion criteria. Based on the outcome of the literature survey, it was possible to perform meta-analysis for escitalopram (N = 2,125), venlafaxine (N = 266), risperidone (N = 1,006), and aripiprazole (N = 824). Drug exposure head-to-head comparisons were made between PM or IM subjects and the NM subject group, which served as a reference. Heterogeneity across the studies was assessed using Cochran's Q test at a given significance level and the percentage of total variability across the studies attributable to heterogeneity was quantified by using I-square value.

Results: The magnitude of the drug exposure increase in comparison to NM is presented as Odds ratio [95% Confidence interval]. Escitalopram exposure was 1.37-fold [1.30-1.44] increased in CYP2C19 IM and 2.44-fold [2.27-2.61] increased in CYP2C19 PM. Venlafaxine exposure was not significantly changed in CYP2D6 PM, 1.10 [0.99-1.22]. Risperidone and aripiprazole exposure increase was similar for CYP2D6 IM and PM. Risperidone exposure was 1.42 [1.36-1.51] increased in CYP2D6 IM and PM admixed. Aripiprazole exposure was 1.52 [1.45-1.58] increased in CYP2D6 IM and PM admixed.

Conclusions: According to the results, (1) reducing escitalopram dose by 60% in CYP2C19 PM and by 30% in CYP2C19 IM are appropriate dosing decisions, (2) reducing risperidone and aripiprazole dose by 30% in CYP2D6 PM is appropriate dosing decision, and (3) CYP2D6 metabolizer status does not seem to be a clinically relevant feature in venlafaxine dosing.

Keywords: Antidepressant, Antipsychotic, Pharmacokinetics, Pharmacogenetics, Precision Medicine Neuropsychiatric Diseases

Disclosure: Nothing to disclose.

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Neurofilament Light Protein as Potential Biomarker of Treatment Resistant Major Depression

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Background: Treatment resistant major depression is