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Pharmacogenetics of glutamate system genes and SSRI-associated sexual dysfunction

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Abstract

We examined whether polymorphisms in the *GRIK2*, *GRIA3*, and *GRIA1* genes were associated with SSRI-associated sexual well-dysfunction in 114 participants treated for depression. One polymorphism in *GRIA1* (rs1994862) was associated with arousal dysfunction, providing further evidence for the role of *GRIA1* in mechanisms underlying SSRI-associated sexual side effects.

Keywords

Antidepressant; single nucleotide polymorphism; sexual dysfunction

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are currently first line antidepressant therapies for the treatment of Major Depressive Disorder (MDD) (Gelenberg, 2010). Unfortunately, a high proportion of patients choose to discontinue their medication due to adverse effects (Bull et al., 2002a; Bull et al., 2002b; Rush et al., 2006) with sexual dysfunction reported as a common bothersome outcome from these medications (Hu et al., 2004) and an estimated prevalence of 20–70% (Bishop et al., 2009; Montejo et al., 2001).

Previous studies suggest that the excitatory neurotransmitter, glutamate, is involved in depression (Hashimoto et al., 2007; Schiffer and Heinemann, 2007) as well as antidepressant-associated suicidal ideation (Laje et al., 2007) and may be involved with sexual functioning (Dominguez et al., 2006; Perlis et al., 2009; Wu et al., 2009). Single nucleotide polymorphisms (SNPs) in genes that code for glutamate receptors, most notably *GRIA3* (glutamate receptor, ionotropic, AMPA3), *GRIK2* (glutamate receptor, ionotropic,

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kainate2), and *GRIA1* (glutamate receptor, ionotropic, AMPA1), are associated with decreased libido and difficulty with orgasm in individuals treated with the SSRI citalopram as indicated by a secondary analysis of the STAR*D effectiveness study (Perlis et al., 2009). The purpose of our study was to extend this area of research by investigating the relationship between selected *GRIK2, GRIA3* and *GRIA1* SNPs in a unique study sample with minimal medication and medical comorbidities to determine whether there is further support for the role of these genes in SSRI-associated sexual difficulties.

2. Methods

2.1 Participants

Samples analyzed for this study were collected as part of a previously enrolled and evaluated cohort of participants (Bishop et al., 2009). Potential participants were 18–40 years old, taking an SSRI medication for least 6-weeks, and free from any kind of sexual dysfunction before they started therapy. Exclusion criteria included other medications, psychiatric, neurologic, or medical conditions that affect sexual functioning. Of 125 participants enrolled, 11 were excluded from analyses due to confounding factors for a total of 114 included in this report. This population had a mean age of 26.3±5.7 years, mean treatment duration of 18±26 months, and 105 (92%) were Caucasian. Thirty (26%) reported using alcohol >5 times in past month and 13% (n=15) were self-reported smokers.

2.2 Assessments

Recruitment and clinical assessments were completed at the University of Iowa, with laboratory assessments and analyses for the present study conducted at the University of Illinois at Chicago College of Pharmacy Pharmacogenomics Laboratory. Depression severity was evaluated with the 21-item version of the Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A). Mean HAM-D and HAM-A scores in participants were 5.9±3.2 and 5.8±3.0, respectively. SSRI utilization was as follows: citalopram (n=14), escitalopram (n=36), fluoxetine (n=25), paroxetine (n=11), and sertraline (n=28). Dose strata were created with “Higher” doses defined as ≥ 40mg/day of citalopram, fluoxetine, or paroxetine; ≥100mg/day of sertraline, and ≥20mg/day escitalopram. Using this characterization, 42 (37%) of participants were taking higher doses of SSRI. Vital signs, height and weight, marital status, race, use of illicit drugs or alcohol, education, smoking habits, and family composition were also collected. The primary outcome assessed in this study was sexual dysfunction defined as a dichotomous measure by sex-specific thresholds on the Changes in Sexual Functioning Questionnaire (CSFQ) (Clayton et al., 1997). Secondary outcomes included arousal and orgasm subscale measures which were also analyzed as dichotomous variables with dysfunction defined by previously validated cut-off scores. All analyses included sex and HAM-D scores as covariates. The decision to use the previously validated categorical outcomes allowed us to analyze males and females together while also providing the opportunity to investigate sex by genotype interactions to guide stratified analyses if necessary.

2.3 Genotyping

Genomic DNA from participants was extracted from buccal cell samples using a standard method (Richards et al., 1993). DNA was amplified by the whole genome amplification technique, using the REPLI-g midi kit (Qiagen, CA). The following SNPs were genotyped using Pyrosequencing™ Technology: *GRIK2* (rs9404130, rs513216), *GRIA3* (rs2285127, rs2269551, rs550640), and *GRIA1* (rs1994862, rs10515697, rs1864205). Direct sequencing was performed to validate our assays. Additionally 15% of samples were genotyped in duplicate to assess genotyping precision. Genotyping calls were made blinded to clinical

variables. Concordance between Pyrosequencing duplicates as well as direct sequencing was 100%.

2.4 Statistical Analyses

Non-genetic analyses were conducted using SAS JMP® software version 8.0.2 (SAS Institute Inc, Cary, NC). Univariate logistic regression analyses were completed to identify associations between clinical variables and sexual dysfunction as measured by falling below sex-specific CSFQ thresholds. Hardy Weinberg Equilibrium (HWE), allele frequency, and genotype associations were assessed with PLINK software (see Table 3) (Purcell et al., 2007). The rs1864205 SNP deviated from HWE and was not included in subsequent analyses. Genotype associations with sexual dysfunction on the CSFQ total, arousal, and orgasm scales were conducted with logistic regression in PLINK assessing additive, dominant, and recessive models controlling for sex and HAM-D scores as well as assessing the significance of sex by genotype interaction terms. The mperm 1000 permutations option in PLINK was selected to control for multiple testing. Our primary analyses included all participants with a post hoc examination in Caucasian subjects.

3. Results

There was no evidence for association between *GRIK2*, *GRIA1*, and *GRIA3* SNPs and depressive symptoms as measured by HAMD scores. Significant relationships between candidate SNPs and the primary outcome of dysfunction as measured by CSFQ total score thresholds were not observed (see Supplementary Tables). In secondary analyses, one SNP (*GRIA1* rs1994862) was significantly associated with arousal dysfunction after controlling for multiple comparisons ($P<0.05$). The rs1994862_CC genotype (n=13 participants) was associated with a lower risk for arousal dysfunction (OR=0.16, 95% CI 0.02, 0.8) than CG or GG participants. There was no evidence for significant genotype by sex interactions ($P>0.05$ for all interaction terms). When Caucasians only were examined, the association of this SNP with arousal dysfunction remained in the same direction at a similar effect size, although at a trend level of significance (OR=0.19, 95% CI 0.03–1.2). Unadjusted results for rs550640 (p=0.07 on the arousal subscale), rs513216 (p=0.08 on total score, p=0.13 on the orgasm subscale), and rs9404130 (p=0.10 on the orgasm subscale) were suggestive of relationships for further study.

4. Discussion

We did not find an association between our candidate SNPs and sexual dysfunction in our primary assessment of CSFQ total scores. However, an association was observed in secondary analyses of dysfunction on the arousal subscale. This SNP was also significantly associated with aspects of sexual dysfunction in a previous study investigating glutamate system SNPs (Perlis et al., 2009). These results provide further evidence that a common SNP in the *GRIA1* gene (rs1994862) may be associated with sexual dysfunction in patients taking an SSRI for depression.

The mechanisms underlying the role(s) of glutamate gene variants in pathways influencing sexual well-being are still under investigation. The rs1994862 SNP resides in the *GRIA1* gene which maps on to chromosome 5q33.1. The function of this intronic variant is not known. It is plausible that this polymorphism in *GRIA1* is in linkage disequilibrium with a causal variant influencing glutamate signaling with direct influence on these outcomes.

Put in the context of previous analyses of glutamate system genes and SSRI-associated sexual dysfunction in the STAR*D study (Perlis et al., 2009), our results lend further support of the importance of the rs1994862 SNP as a marker of SSRI-associated sexual

dysfunction. These results must be interpreted in the context of the limitations of our study. To this end, we observed statistically significant effects only when we included all 114 participants in our analysis. In a *post hoc* analysis of Caucasians only the effect size was maintained with a p-value at the trend level of significance. This likely illustrates that our sensitivity to detect significant associations was limited by our sample size. We utilized sex-specific thresholds for sexual dysfunction, which allowed us to group males and females together. We controlled for sex in our analyses and did not find evidence for significant sex by gene interactions. However, we were not adequately powered to conduct stratified analyses in both males and females which are important for future studies to consider. Another limitation is that a point prevalence study design may not be as optimal as a prospective analysis to identify treatment-emergent effects. However, we feel that our strategy of excluding those reporting sexual difficulties before treatment was useful in characterizing the relationship between genetic variants and sexual dysfunction in the context of SSRI treatment in patients who had minimal clinical symptoms, thus increasing our ability to isolate the sexual side effect phenotype using the CSFQ. Finally, our criterion of SSRI utilization for at least 6 weeks was designed to minimize the effects of the depression on sexual functioning, but this may have also resulted in missing participants who may have discontinued treatment earlier.

5. Conclusion

We report an association between a common polymorphism in *GRIA1* with sexual dysfunction on the arousal subscale of the CSFQ in patients treated with an SSRI for depression. These results are consistent with previous findings. This suggests an important role for glutamate signaling in SSRI-associated sexual dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Genotype associations between selected glutamate SNPs and SSRI-associated sexual dysfunction on CSFQ[A] arousal scores[B]

Gene	SNP	Position[C]	Location	Alleles	MAF[D]	HW[E] pval	P-value[F]	P-value (adjusted)[G]
GRIA1	rs1994862	152969103	Intron	C:G	0.32 (G)	0.67	**0.02**	**0.03**
GRIK2	rs513216	102165584	Intron	A:G	0.31 (G)	0.12	0.35	0.64
GRIK2	rs9404130	102282474	Intron	C:G	0.07 (G)	0.068	0.93	1.0
GRIA3	rs2269551	122147598	Intron	G:A	0.32 (A)	0.076	0.55	0.99
GRIA3	rs2285127	122164129	Intron	G:A	0.32 (A)	0.45	0.26	0.79
GRIA3	rs550640	122356484	Intron	A:G	0.36 (G)	1.0	0.07	0.32

[A] Changes in Sexual Functioning Questionnaire (CSFQ)

[B] Additive, recessive, and dominant logistic regression models were tested controlling for Hamilton Depression Rating Scale (HAMD) scores and sex as covariates. The model best fitting each SNP is included.

[C] Genome build 36.3

[D] MAF : Minor Allele Frequency

[E] HWE : Hardy Weinberg Equilibrium

[F] Empirical point-wise P-value after permutation.

[G] P-values adjusted for multiple comparisons taking into account the number of SNPs assessed and linkage disequilibrium between SNPs using permutation analyses.