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Genetic variation in the serotonin transporter and HTR1B receptor predicts reduced bone formation during serotonin reuptake inhibitor treatment in older adults

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Abstract

Objectives—Studies have reported an association between serotonin reuptake inhibitors (SRIs) and accelerated bone loss. Genetic variation in the serotonin system might modulate bone metabolism changes during SRI treatment. In a clinical trial we examined functional genetic polymorphisms of serotonin transporter and receptors involved in bone metabolism to determine whether they predict changes in bone metabolism during SRI treatment.

Methods—In 69 adults (age ≥ 60) participating in a 12-week, open-label trial of the SRI venlafaxine for major depression, serum markers of bone formation (P1NP) and resorption (β-CTX) were assayed before and after treatment. Participants were genotyped for putative high- versus low-expressing polymorphisms in the serotonin transporter (5HTTLPR) and 1B receptor (HTR1B) genes.

Results—Bone formation was significantly reduced with administration of venlafaxine in participants with the high-expressing 5HTTLPR genotype and those with the low-expressing HTR1B genotype. This primarily occurred in individuals with the combination of the high-expressing 5HTTLPR genotype and the low-expressing HTR1B genotype.

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Statement of Interest

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Conclusions—These preliminary findings indicate that genetic variation in the serotonin receptors predicts changes in bone metabolism during SRI use. If these results are replicated and clinically confirmed, we will have identified a genetic subgroup at high risk for deleterious bone outcomes with the use of SRIs.

Keywords

pharmacogenetics; serotonin; bone diseases; biological markers; aged

Introduction

There is evidence that serotonin reuptake inhibitors (SRIs) negatively affect bone metabolism from experimental studies in rodents and (Westbroek et al. 2007; Warden et al. 2008, 2010a) epidemiological studies in humans (Diem et al. 2007; Haney et al. 2007, 2010; Richards et al. 2007). The potential public health impact of this link is large given that antidepressants are the most commonly prescribed class of medication in the United States (Olfson and Marcus 2009) and the significant human and economic burden of osteoporosis (Dempster 2011). Older adults are at increased risk for serotonin-related bone loss due to ageing-related risk of osteoporosis and fractures (Looker et al. 2012). There is some suggestion that SSRIs inhibit bone cell formation and function (Hodge et al. 2012); more evidence for the association between serotonin and bone metabolism would strengthen this association. (Shea et al. 2013).

Serotonin receptors are expressed on bone cells and modulate bone metabolism. Osteoblasts express both the serotonin transporter (5HTTLPR) and the serotonin 1B receptor (HTR1B) (Bliziotes et al. 2001, 2006; Gustafsson et al. 2006; Collet et al. 2008; Yadav and Ducy 2010). Thus, it is biologically plausible that SRIs would affect bone metabolism via these receptors. Pre-clinical studies suggest that 5HTTLPR and HTR1B are key serotonin signalling molecules for bone formation (Yadav et al. 2008; Yadav and Ducy 2010); Therefore, they are top candidates for mediating the effects of SRIs on bone health and there may be individuals at greater risk for negative bone outcomes from SRIs due to functional genetic variability in serotonin transporter and receptors.

In this study, we focused on two promoter polymorphisms: the tri-allelic 5HTTLPR polymorphism in SLC6A4 (serotonin transporter gene) and rs11568817 SNP in HTR1B. The 5HTTLPR polymorphism has been extensively studied in psychiatric genetic studies (Kenna et al. 2012) and the functional relevance of both gene variants are well established (Conner et al. 2010; Kenna et al. 2012). We examined change in bone turnover markers (BTMs), by-products of natural processes of bone formation and resorption that can be measured in serum. Bone formation can be measured via amino-terminal propeptide of type I collagen (P1NP) released by osteoblasts, while bone breakdown or resorption can be measured via C-telopeptide of type I collagen (β-CTX) released by osteoclasts. These BTMs are advantageous in a clinical trial because they allow for measurement of change in bone metabolism over a shorter time course than bone mineral density (BMD); changes in BTM over time can be used to monitor changes in bone turnover and the effect of treatment (Black et al. 2007; Cummings et al. 2009; Lewiecki 2010). We examined the association of

change in the BTMs P1NP and β-CTX during treatment, with genetic variation in the promoter regions of 5HTTLPR and HTR1B.

Materials and methods

Participants

We obtained data from a prospective treatment study of late-life depression conducted at three academic sites (University of Pittsburgh, University of Toronto/Centre for Addiction and Mental Health, Washington University) (Joel et al. in press) in 2009–2011. The institutional review boards at the three participating institutions approved the study protocol and all participants provided written informed consent. Participants were aged 60 and older and presented with a current major depressive episode of 4 weeks duration or longer. Depression diagnosis was established using the Structured Clinical Interview for DSM-IV Axis-I disorders (First et al. 1996) and a score ≥ 15 on the Montgomery–Asberg Depression Rating Scale (MADRS), indicating at least moderate depressive symptoms (Montgomery and Asberg 1979). We excluded participants with diagnoses of lifetime bipolar disorder, chronic psychotic disorder or dementia, history of alcohol or substance abuse or dependence during the past 6 months, unstable medical illness, corticosteroid treatment, or any contraindication to venlafaxine. We assayed BTMs in participants who completed the acute treatment phase and both pre- and post- serum collections within the recommended 08:00 to 11:00 h time-frame for biomarker collection (Nishizawa et al. 2005; Civitelli et al. 2009; Shea et al. 2013). Twenty-eight patients were receiving an SSRI prior to entering the study and discontinued this drug 2 weeks prior to beginning the open-label study treatment. Analyses were conducted in European-Americans only for various reasons: First, differences in bone metabolism were described varying among different populations (e.g., Crandall et al. 2012). Second, the allele frequencies typically vary among ethnic groups (Gelernter et al. 1997) and population stratification may result in spurious findings. Lastly, the excluded group of African-Americans was small and not in Hardy–Weinberg equilibrium, for which reason we decided to not consider this group for combined or separate exploratory analyses.

Venlafaxine pharmacotherapy

All participants received open-label venlafaxine extended release capsules (XR) for 12 weeks. Venlafaxine is primarily a SRI, with approximately 100-times greater potency of serotonin than norepinephrine transporter binding (O'Donnell and Shelton 2011). Venlafaxine was started at 37.5 mg/day and titrated over 2 weeks to a target dose of 150 mg/day. After 6 weeks, those who did not achieve remission (MADRS ≤ 10) had their dose increased to a maximum of 300 mg/day; those in remission at week 6 maintained a dose of 150 mg/day. We measured adherence to venlafaxine by asking participants to report the number of pills they missed since the previous visit. Self-reported adherence was high: participants reported missing no pills during 93% of study visits, and 1–4 missed pills since the prior visit during 7% of visits. Adherence was independently confirmed with blood levels and pill counts. One participant with no detectable serum venlafaxine level ($n = 1$) was assumed to be non-adherent and excluded from all analyses.

Serum measures

Blood samples were collected after an overnight fast and prior to 11:00 h, before beginning venlafaxine treatment and at the end of 12 weeks of treatment. Samples were immediately cold-centrifuged and stored at −80°C until analysis.

Genotyping

DNA was extracted from blood using standard procedures. For 5HTTLPR polymorphisms we followed a procedure that genotypes two promoter polymorphisms: the insertion/deletion polymorphism (L/S) and A/G SNP at rs25531 (Wendland et al. 2006). These two polymorphisms are combined as Sa, Sg, La, and Lg, in which only the La combination is considered high-expressing (Hu et al. 2006; Steiger et al. 2007; Frodl et al. 2008; Dombrovski et al. 2010;Thakur et al. 2010; Wankerl et al. 2010; Beevers et al. 2011); we treated La/La, La/S, or La/Lg genotypes as high-expressing and S/S, S/Lg or Lg/Lg genotype as low-expressing. For HTR1B, we used the Sequenom™ technology to examine rs11568817, a putatively functional single nucleotide polymorphism (SNP) in the promoter region where GG or GT genotype is considered high-expressing and TT is considered low-expressing (Lenze et al. 2013).

Bone metabolism

We assayed two serum measures of bone turnover: P1NP, a measure of bone formation; and β-CTX, a measure of bone resorption. P1NP was measured using radioimmunoassay (RIA; Core Diagnostics) with intraassay coefficient of variation (CV) of 6.1–7.9% and interassay CV of 4.3–4.7%. β-CTX was measured with electrochemiluminescence immunoassay (β-Crosslaps/serum, Core Diagnostics) with intraassay CV of 1.0–1.3% and interassay CV of 1.1–1.6%.

Venlafaxine concentration

Both serum venlafaxine and its metabolite, norvenlafaxine were measured using a liquid chromatography/mass spectrometry protocol developed at the Centre for Addiction and Mental Health Clinical Laboratory with the TSQ (triplequadrupole) mass spectrometer (ThermoFisher) as described previously (Shea et al. 2013). Both intra- and interassay CV were < 10%.

Statistical analysis

A series of *t*-tests and chi square tests were used to assess differences for demographic or clinical covariates. In a first pass, to determine if there was an overall change in bone formation (P1NP) or resorption (β-CTX) due to venlafaxine treatment, we compared changes in mean biomarker level in high- and low-expressing genetic groups using the robust Wilcoxon's matched pair signed rank test. We then used mixed models to examine the effect of either 5HTTLPR or rs11568817 high-activity genotypes on bone metabolism while controlling for several potential confounders: gender, use of bisphosphonates or estrogen, use of an SSRI prior to study entry, and final venlafaxine concentration. Finally, we used mixed models to examine the combined effect of both 5HTTLPR and rs11568817

high-activity genotypes. All analyses were computed using SAS 9.2 (SAS Institute, Cary, NC).

Results

Sixty-nine participants met all eligibility criteria and comprise the study group; they were from the open-label lead-in phase of an NIH-funded pre/post RCT augmentation study. They include all participants who completed this phase and met criteria for bone biomarker collection. There were no statistically significant associations between high- and low-expressing 5HTTLPR or 5HTR1B genotypes and demographic or clinical characteristics (Table I). Participants had a mean (SD) age of 69.0 (7.1) years and 62% were female. They had a mean (SD) body mass index (BMI) of 30.4 (7.0) at baseline and had a mean (SD) baseline MADRS score of 26.8 (5.8) indicating a clinical depression of moderate severity; 12% were receiving a bisphosphonate or an estrogen supplement during the study with no change during the treatment period. At the conclusion of the 12-week treatment period the mean (SD) improvement in MADRS score was 10.7 (9.7) with a mean (SD) decrease in BMI of 0.9 (3.5). Participants reached a mean (SD) final venlafaxine dose of 252.2 (64.0) mg/day.

There were significant differences in change in bone formation (P1NP) for both 5HTTLPR and HTR1B genotypes (Table II). Over the 12-week study, participants with the high-expressing 5HTTLPR genotype (carriers of the LA allele) had a statistically significant decrease in P1NP (mean change ± SD: −4.1 ± 15.7; $P = 0.02$ in contrast to non-carriers in whom the change was not statistically significant (0.2 ± 19.8; $P = 0.74$). Similarly, carriers of the lower activity G allele on rs11568817 of the HTR1B gene experienced a statistically significant P1NP decrease from baseline (−4.9 ± 13.0; $P = 0.04$ in contrast to non-carriers (1.6 ± 18.4; $P = 0.30$). These analyses suggested time by genotype interaction effects, which were confirmed using mixed models, adjusting for gender, use of bisphosphonates or oestrogen, previous SSRI use, and final venlafaxine concentration (data not shown, $P < 0.05$). These analyses confirm that the magnitude of P1NP decrease was significantly higher in participants with either the high activity La for 5HTTLPR or the low-activity G allele for rs11568817 ($P < 0.05$ for both).

We then investigated whether the combination of both La and G was associated with the highest decreases in P1NP (Table II). We found the greatest decrease in bone formation (decrease in P1NP) in the group with combined high-expressing 5HTTLPR, low-expressing HTR1B genotype: the 13 participants with this combined genotype showed a mean (SD) decrease in P1NP of −7.4 (10.4) ($P = 0.02$), numerically larger than for any other combination of genotypes. The effect remained significant after controlling for gender, previous SSRI exposure, treatment with bisphosphonates or oestrogen, and final venlafaxine dose in mixed effect models (data not shown, $P < 0.05$).

Neither genotype appeared to affect bone resorption, as measured by β-CTX change from baseline to follow-up by genotype (data not shown; all $P > 0.10$). Similarly, there were no significant changes in bone resorption for the combined genotypes group.

Discussion

The goal of this analysis was to determine if there are sources of genetic variability associated with 5HTTLPR or HTR1B that influence the effect of SRI treatment on bone metabolism in depressed older adults. We found that the high-expressing 5HTTLPR genotype (i.e. carriers of La) and the low-expressing genotype for rs11586617 in HTR1B (i.e. TT genotype) predicted greater decrease in bone formation. The greatest decrease in bone formation was found in participants who possessed both of these “at risk” genotypes. Moreover, there appeared to be no compensatory decrease in bone resorption (i.e. reduction in β-CTX) to offset the changes in bone formation observed in these genetic groups. The decrease in bone formation remained significant after controlling for important confounders including gender, treatment with medications affecting bone metabolism (oestrogen or bisphosphonates), SSRI exposure prior to study entry, and final venlafaxine dose. There was no evidence for bias in terms of demographic or clinical characteristics between participants with different genotypes; thus, it does not appear that the observed differences were due to differences in change in body weight or depression treatment.

This finding of genetically moderated SRI effects on bone formation fits with current understanding of the biology of the serotonin system with respect to bone metabolism. Serotonin has separate central and peripheral systems, segregated by the blood–brain barrier. The serotonin transporter, the proximal drug target of SRIs, is found on all bone cells types including osteoblasts. Osteoblasts also express HTR1A, 1B, 1D, 2A and 2B (Battaglino et al. 2007; Bliziotes et al. 2001, 2006; Collet et al. 2008; Gustafsson et al. 2006; Westbroek et al. 2001; Yadav et al. 2008). While the mechanism by which serotonin acts on bone remains undetermined, Yadav et al. (2008) showed that HTR1B knockout mice have an increased number of osteoblasts on bone surfaces and accelerated bone formation rates, suggesting that serotonin may inhibit osteoblast proliferation via the HTR1B receptor (Haney et al. 2010; Warden et al. 2010b). A role for other receptors has not been excluded (Bliziotes 2010). In a recent review Bliziotes (2010) postulates that the pathway for skeletal effect of SRIs via serotonin transporter may be direct inhibition of transporters on bone cell membranes, increasing local serotonin level. Our results are consistent with a peripheral serotonin mediation of observed genetic effects on bone metabolism. There is also recent evidence that centrally derived serotonin affects bone mass as Karsenty and Yadav (2011) observed a severely osteoporotic phenotype in mice created unable to synthesize brain serotonin; it is unclear whether genetic results would be consistent with this recent finding. Brain-derived serotonin may be linked to decreased bone mass through leptin. Leptin and brain serotonin have the same peripheral mediator, the sympathetic nervous system, and thereby leptin appears to inhibit serotonin synthesis or release by brain neurons, via the 5HT2C receptor (Karsenty and Oury 2010). Polymorphisms in this gene may be another source of variability of SRI-induced bone turnover change, and future studies should examine this possibility. Finally, Calarge et al. (2011) have shown preliminary evidence of a pharmacogenetic effect in a cross-sectional study of SSRI treated adolescent males, with those having one copy of the low-expressing 5HTLLPR genotype showing lower trabecular and lumbar bone mineral density (BMD).

Strengths

In this pre-post study design, participants served as their own controls. Participants were well-characterized and received protocolized antidepressant treatment with adherence confirmed both by self-report and drug-levels. We measured BTMs both before and after treatment and accounted for factors known to be associated with bone metabolism. We found congruent results using both bivariate and multivariate statistical methods and looking at individual and combined genotypes.

Limitations

This study had a small sample size of 69 patients who completed treatment and had complete bio-marker and genetic data. This may affect our ability to detect significant associations (type 2 error), such as our lack of significant findings for β-CTX. Given the open-label treatment study design, we do not have a randomized control group of untreated participants. Therefore, our results should be considered as hypothesis generating and confirming replication studies are needed. It is also not clear whether the changes in BTMs were of a magnitude that would be clinically relevant. The changes in P1NP were of smaller magnitude than one would expect to see with bisphosphonate treatment; however, patients in this study did not experience a concomitant decrease in β-CTX. Therefore the reduction in bone formation may be sufficient to account for the observed relationship between SRIs and bone loss (Diem et al. 2007). Future studies with multiple biomarkers would be stronger as would examination of additional outcomes such as bone loss or fractures; this will require much larger samples followed over longer periods of time.

Conclusion

To our knowledge, this is the first experimental study to show pharmacogenetic effects on bone metabolism with SRI treatment. It provides proof of the concept that SRIs reduce bone formation in subjects with specific genetic traits. However, even assuming that future, larger studies confirm that SRIs adversely affect bone health, it is not likely that prescription of these drugs would stop given the impact of untreated depression and anxiety disorders on quality of life, function, and general health. Therefore, the potential application of this finding, upon confirmation in other samples and with other SRIs, could be the personalization of SRI therapy in order to protect those at highest risk of deleterious bone effects, thus improving the safety of this effective and important treatment for depression. Future work with existing serum samples and genotype data from larger, phase III randomized controlled trials would be a logical next step to confirm these findings.

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Table I

Characteristics of 69 older adults with current major depressive episode, at baseline, overall and by 5HTTLPR and HRT1B expression status.

	Total sample (*n* = 69)	5HTTLPR high expressing (*n* = 45)	5HTTLPR low expressing (*n* = 22)	*P* value	HTR1B high expressing (*n* = 45)	HTR1B low expressing (*n* = 21)	*P* value
Age, mean (SD)	69.0 (7.1)	69.0 (6.9)	68.4 (7.3)	0.76	69.2 (6.8)	68.3 (7.5)	0.61
Gender, *n* (%Female)	43.0 (62.3)	27.0 (60.0)	14.0 (63.6)	0.77	29.0 (64.4)	12.0 (57.1)	0.57
Baseline MADRS, mean (SD)	26.8 (5.8)	26.8 (5.7)	25.6 (4.9)	0.38	26.2 (5.2)	26.9 (6.2)	0.64
MADRS score change, mean (SD)	−10.7 (9.7)	−9.9 (10.3)	−11.2 (7.2)	0.58	−10.8 (8.2)	−9.7 (11.8)	0.70
RBANS, mean (SD)	96.2 (17.4)	97.6 (16.3)	94.8 (19.1)	0.53	96.4 (15.9)	97.8 (20.7)	0.78
Baseline BMI, mean (SD)	30.4 (7.1)	30.6 (7.8)	30.0 (5.5)	0.74	30.4 (6.7)	29.7 (7.4)	0.74
BMI score change, mean (SD)	−0.86 (3.5)	−0.9 (4.1)	−0.8 (1.9)	0.85	−0.4 (1.2)	−1.6 (5.7)	0.39
Pre-study SSRIs, *n* (%)	28.0 (40.6)	20.0 (44.4)	8.0 (36.4)	0.53	19.0 (42.2)	8.0 (38.1)	0.75
Final Venla dose mg, mean (SD)	252.2 (64.0)	257.5 (61.7)	240.3 (74.1)	0.31	253.3 (66.0)	246.4 (63.4)	0.69
Final Norvenal conc ng/ml, mean (SD)	320.1 (157.9)	326.3 (159.4)	310.1 (164.8)	0.70	324.6 (167.1)	310.6 (151.3)	0.75
Final Venla conc ng/ml, mean (SD)	193.7 (177.8)	214.0 (196.8)	156.1 (135.1)	0.22	209.9 (189.3)	161.8 (162.1)	0.32
Any bone meds, *n* (%)	23.0 (33.3)	17.0 (37.8)	5.0 (22.7)	0.22	16.0 (35.6)	5.0 (23.8)	0.34
Bisphosphonate or Estrogen, *n* (%)	8.0 (11.6)	7.0 (15.6)	1.0 (4.6)	0.26	7.0 (15.6)	1.0 (4.8)	0.21

MADRS, Montgomery–Asberg Depression Rating Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; BMI, body mass index; SSRIs, selective serotonin reuptake inhibitors; Venla, venlafaxine; Norvenla, norvenlafaxine; Any bone meds: includes bisphosphonates, calcium, vitamin D and estrogen.

Table II

Mean change in bone biomarkers (P1NP, CTX) by individual and combined genetic groups for 69 older adults treated with venlafaxine XR for 12 weeks.

		P1NP		CTX	
	n	**Mean change (SD)**	**Wilcoxon matched pair signed rank test *P* value**	**Mean change (SD)**	**Wilcoxon matched pair signed rank test *P* value**
Serotonin transporter 5HTTLPR					
High-expressing (LA = 1 or 2)	45	−4.1 (15.7)*	0.02	22.6 (165.8)	0.22
Low-expressing (LA = 0)	22	−0.2 (19.8)	0.74	35.7 (0.1)	0.13
HRT1B receptor rs11568817 SNP					
High-expressing (GG/GT)	45	−1.6 (18.4)	0.30	18.4 (185.5)	0.26
Low-expressing (TT)	21	−4.9 (13.0)*	0.04	40.8 (185.5)	0.20
Combined genotypes					
5HTTLPR high + HTR1B high	31	−2.4 (11.2)	0.27	7.2 (128.1)	0.75
5HTTLPR high + HTR1B low	13	−7.4 (10.4)*	0.02	51.9 (94.9)	0.14
5HTTLPR low + HTR1B high	14	0.3 (10.8)	0.86	43.1 (90.8)	0.09

*$P < 0.05$.