Clock Gene Modulates Roles of OXTR and AVPR1b Genes in Prosociality

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Abstract

Background: The arginine vasopressin receptor (AVP) and oxytocin receptor (OXTR) genes have been demonstrated to contribute to prosocial behavior. Recent research has focused on the manner by which these simple receptor genes influence prosociality, particularly with regard to the AVP system, which is modulated by the clock gene. The clock gene is responsible for regulating the human biological clock, affecting sleep, emotion, and behavior. The current study examined in detail whether the influences of the OXTR and AVPR1b genes on prosociality are dependent on the clock gene.

Methodology/Principal Findings: This study assessed interactions between the clock gene (rs1801260, rs6832769) and the OXTR (rs1042778, rs237887) and AVPR1b (rs28373064) genes in association with individual differences in prosociality in healthy male Chinese subjects (n=436). The Prosocial Tendencies Measure (PTM-R) was used to assess prosociality. Participants carrying both the GG/GA variant of OXTR (rs28373064) and the AA variant of clock rs6832769 showed the highest scores on the Emotional PTM. Carriers of both the T allele of OXTR rs1042778 and the C allele of clock rs1801260 showed the lowest total PTM scores compared with the other groups.

Conclusions: The observed interaction effects provide converging evidence that the clock gene and OXT/AVP systems are intertwined and contribute to human prosociality.

Introduction

Increasing evidence suggests that circadian rhythms are important regulatory processes. Most organisms form and maintain daily patterns of behavior to adapt to 24-h cycles of light and temperature in their environment [1,2]. The molecular mechanisms of the circadian cycle involve at least 9 core circadian genes that control transcriptional and translational feedback loops [3], encoding activator and repressor proteins. Among these circadian genes, the circadian locomotor output cycles kaput (clock) gene is transcribed to produce the CLOCK protein, which is an essential element of the circadian pacemaker that plays a vital role in regulating human biological timing [4]. The circadian regulatory loop consists of positive elements CLOCK and BMAL1 which bind as a heterodimer to an enhancer element termed the E-box. Notably, to better anticipate and adapt to daily environmental changes, CLOCK:BMAL1 heterodimer expression levels rise to activate the transcription of clock-controlled genes during the day, whereas these levels decrease at night, thereby reducing the transcription of the clock-controlled genes [1,3]. Clock mRNA and protein are constitutively expressed in the suprachiasmatic nucleus (SCN), which is the principle circadian oscillator [5]. Furthermore, the clock gene and SCN-mediated circadian clock output affect sleep and emotion [6]. For example, rs1801260 (3111T/C), which is a SNP located in the 3′-flanking region of the clock gene, has been shown to contribute to bipolar disorders and sleep disorders, whereas CC carriers are more likely to suffer from both bipolar and sleep disorders [7,8]. Additionally, previous studies have reported that C allele carriers of rs1801260 display more emotional apathy than the TT carriers [9]. Furthermore, the C (minor) allele is associated with evening preference among Caucasian and Asian populations [10,11], with evening hours being favored for novelty-seeking and impulsive activities, which leads to reduced affiliating emotions and prosocial behavior [12]. Moreover, a genome-wide association study by Terracciano et al. [13] indicated that the clock SNPs rs1801260 (3111T/C) and rs6832769 show the strongest associations with prosocial behavior as recognized by agreeableness, which is one of the five broad dimensions of human personality. Because the heritability of prosocial behavior has been emphasized both in twin-designed studies and molecular genetic studies [14,15] and considering the aforementioned evidence, we aimed to explore the relationship between clock gene and prosocial behavior, although little direct evidence exists suggesting that they are linked.

Current knowledge indicates that the core clock mechanism involves E-box-regulated transcription. The transcriptional activators CLOCK and BMAL1 bind as heterodimers to CACGTG...
E-box enhancers located in the promoters of the per, cry, and clock-controlled genes, to modulate the functions of the central clock in the brain [1]. Indeed, the expression levels of many genes are regulated by CLOCK:BMAL1 heterodimers acting through E-box elements [16]. The product of one such clock-controlled gene, arginine vasopressin (AVP), contributes to extracellular signaling and dopamine metabolism, controlling behavioral and neuroendocrine cycles [17]. Among the human vasopressin receptors, the arginine vasopressin V1b receptor (AVPR1b) is important in regulating the responsiveness of pituitary corticotrophins to vasopressin. AVPR1b is expressed primarily in the pituitary and discrete areas of the brain, including the SCN, which is a fundamental area where clock-controlled genes are also expressed [18]. Evidence suggests that the AVPR1b gene is closely related to anxiety and depression [19]. For example, changes in pituitary AVPR1b level contribute to corticotrophin responsiveness under chronic stress, and the up-regulation of the AVPR1b has been suggested in individuals with depression, which could contribute to the shift in the hypothalamic drive from corticotrophin-releasing hormone to AVP [20]. Furthermore, the genotypic variation AVPR1b rs28373064 may disturb the sleep-wake cycle and other circadian rhythms, which may cause problems with vasopressin, thus affecting mood [21]. Because prosociality may serve as a coping strategy for reducing depression and stress [22], we hypothesized that variations in the AVPR1b gene are related to prosociality and that this relation might be modulated by the clock gene.

Oxytocin (OT) is another nonapeptide that shares a similar chemical structure with AVP. The two most important social hormones, AVP and OT, are both nonapeptides synthesized in the hypothalamus and released into the bloodstream via axon terminals in the posterior pituitary or neurohypophysis. Most regions that express AVPR1b mRNA also express oxytocin receptor (OXTR) mRNA [18]. Furthermore, OT and AVP are known to mediate affiliative behaviors in mammals [23]. Recently, OT has increasingly been established as a prosocial neuropeptide in humans due to its close relationship with personal trust, generosity and charitable giving [23]. The OXTR gene contributes to empathy and prosociality. For example, carriers homozygous for the G allele of OXTR rs237887 display more emotional empathy than those with the A allele [24], and GG carriers are also more prosocial than AA carriers [15]. A significant association was also observed with carriers of the G allele of the rs1042778 SNP, who showed higher levels of giving in the dictator game [15]. Feldman et al. [25] showed that the GG genotype of the SNP rs1042778 is associated with increased affiliative behaviors and generosity. In these aforementioned studies, the individuals with the GG genotypes were found to display increased prosociality; thus, it is termed as the “generous” genotype. In contrast, individuals with the A allele exhibited decreased prosociality, and the associated genotype is termed the “mean” genotype. Therefore the genotypes (e.g., AA genotype of OXTR rs1042778) associated with decreased prosociality include the “risk alleles” for prosociality [24,25]. Elstein, Israel, Chew, Zhong, and Knafo [26] have advocated studies exploring gene × gene interactions in prosocial behavior; thus, we hypothesized that the link between the OXTR gene and prosocial behavior may be modulated by the clock gene.

Therefore, to address the impact of gene interactions on prosociality and to clarify the association between the clock gene and prosociality, 2 SNPs of the clock gene (rs1801260 and rs6832769) and an additional 3 SNPs of the OXTR (rs1042778 and rs237887) and AVPR1b (rs28373064) genes were selected. The present study had two hypotheses; first, that the clock gene is closely related to prosociality; and second, that the influences of the OXTR and AVPR1b genes on prosociality are modulated by the clock gene.

Materials and Methods
Participants
In total, 436 healthy male college students were recruited, the mean age was 21.84 (SD = 1.44). The participants first provided buccal swabs for the genotyping of OXTR rs1042778 and rs237887, AVPR1b rs28373064, and clock rs1801260 and rs6832769. Subsequently, all participants completed a paper-and-pencil version of the Prosocial Tendencies Measure (PTM-R). All participants gave written informed consent prior to the study. Upon completion of all tests, a gift was given for their participation. The study was approved by the local ethics committees of Peking University.

Prosocial Tendencies Measure
The PTM-R [27,28] was used to assess six different prosocial behavioral tendencies that tend to vary according to situation (e.g., emergency situations) and motive (e.g., altruism). The 26-item version of the PTM-R was composed of 6 subscales: Public (4 items), Anonymous (5 items), Dire (3 items), Emotional (4 items), Compliant (5 items) and Altruism (4 items). The participants were asked to rate the extent to which the statements described themselves on a 5-point scale ranging from 1 (does not describe me at all) to 5 (describes me greatly). Previous research demonstrated that the Chinese version of the PTM-R has adequate internal reliability and validity [28]. The present study also showed adequate internal reliability for this test, with alpha levels ranging from 0.67–0.82.

Table 1. Mean scores and standard deviations of each component of Prosocial Tendencies Measure.

| PTM (n=436)   | range | Mean | SD  |
|--------------|-------|------|-----|
| Public       | 1–5   | 3.06 | 0.83|
| Anonymous    | 1–5   | 3.55 | 0.71|
| Dire         | 1–5   | 4.00 | 0.70|
| Emotional    | 1–5   | 3.73 | 0.68|
| Compliant    | 1–5   | 3.77 | 0.72|
| Altruism     | 1–5   | 3.98 | 0.68|
| Total PTM    | 6–30  | 22.09| 3.24|

doi:10.1371/journal.pone.0109086.t001

PLOS ONE | www.plosone.org 2 October 2014 | Volume 9 | Issue 10 | e109086
### Table 2. OXTR, AVPR1b and clock SNP genotype frequencies.

| Gene   | SNP                | Genotype     | mAF  | Frequency | p_HWE | Genotype Frequency | Total | p_HWE  | Total |
|--------|--------------------|--------------|------|-----------|-------|--------------------|-------|---------|--------|
|        | rs6832769          | AA/AG/GG     | 0.279| 0.527/0.389/0.084 | 226/167/36 | 429 | 0.515 |        |
| OXTR   | rs28373064         | AA/AG/GG     | 0.146| 0.720/0.269/0.011 | 313/117/5 | 435 | 0.101 |        |
|        | rs1042778          | GG/GT/TT     | 0.075| 0.855/0.140/0.005 | 373/61/2 | 436 | 0.769 |        |
|        | rs237887           | GG/GA/AA     | 0.459| 0.294/0.494/0.212 | 128/215/92 | 435 | 0.922 |        |

Notes: mAF, minor allelic frequency; p, p-value - HWE, of Hardy-Weinberg equilibrium test.

### Results

The descriptive statistics of the PTM-R are presented in Table 1. Table 2 reports the genotype frequencies and information on the number of participants per allelic group, including the minor allele frequencies, number of individuals at each locus and p-values for the Hardy-Weinberg equilibrium test. The genotype distributions of all SNPs of clock, AVPR1b and OXTR were in Hardy-Weinberg equilibrium.

We found a marginal main effect of OXTR rs1042778 on Compliant PTM scores \[ F(1, 434) = 3.35, p = 0.068, \text{partial } \eta^2 = 0.008 \]; T allele (GT & TT) carriers had lower Compliant PTM scores than those with the GG genotype. No main effects of clock rs1801260/rs6832769, AVPR1b rs28373064 and OXTR rs237887 on the PTM-R or its subscales were detected.

Analysis of covariance models revealed a significant interaction effect of AVPR1b rs28373064 and clock rs6832769 on the Emotional PTM \[ F(1, 425) = 3.35, \text{partial } \eta^2 = 0.011 \], and significance was maintained after Bonferroni correction for multiple testing. Prosociality under emotionally evocative situations for the participants with combined genotype configuration of G+/G− (i.e., GG or GA for AVPR1b rs28373064 and AA for clock rs6832769, \( M_{G+G−} = 3.91, SD_{G+G−} = 0.68, n = 62 \)) was the highest compared with the other groups \( \langle M_{G+G−} = 3.66, SD_{G+G−} = 0.77, n = 59; M_{G−G−} = 3.74, SD_{G−G−} = 0.66, n = 144; M_{G−G+} = 3.67, SD_{G−G+} = 0.64, n = 164 \rangle \); see Figure 1).

There was a statistically significant interaction between OXTR rs1042778 and clock rs1801260 with regard to total PTM scores \[ F(1, 432) = 5.18, p = 0.026, \text{partial } \eta^2 = 0.012 \], which was maintained following Bonferroni correction for multiple testing. Carriers of the genotype configuration T+/C+ (i.e., GT or TT for OXTR rs1042778 and CT or CC for clock rs1801260) showed the lowest total PTM scores \( M_{T+T+} = 19.00, SD_{T+T+} = 3.22, n = 7 \) compared with the other groups \( \langle M_{T+T−} = 21.90, SD_{T+T−} = 3.13, n = 56; M_{T−T+} = 22.32, SD_{T−T+} = 3.08, n = 60; M_{T−T−} = 22.12, SD_{T−T−} = 3.24, n = 313 \rangle \); see Figure 2). Further testing revealed that the interaction involving the total PTM scores was influenced mainly by the Anonymous PTM \[ F(1, 432) = 5.01, p = 0.026, \text{partial } \eta^2 = 0.011 \] and Emotional PTM \[ F(1, 432) = 3.94, p = 0.048, \text{partial } \eta^2 = 0.009 \].

An additional interaction of OXTR rs237887 and clock rs6832769 on Public PTM was also detected \[ F(1, 424) = 4.63, p = 0.032, \text{partial } \eta^2 = 0.011 \], indicating that allele A (AA/AG) of OXTR rs237887 was associated with higher Public PTM scores \( \text{Bonferroni } p = 0.049, \text{partial } \eta^2 = 0.009 \) only for those individuals with the clock rs6832769 AA genotype. However, this association...
was not found for the G allele carriers (GG/GA) of clock rs6832769 (Bonferroni p = 0.288, partial $\eta^2 = 0.003$; Table 3).

**Discussion**

In the present study, we observed interaction effects of AVPR1b rs28373064 and clock rs6832769, OXTR rs1042778 and clock rs1801260, and OXTR rs237887 and clock rs6832769 on prosociality. These findings suggest that the influences of AVPR1b and OXTR on prosociality are dependent on the genetic variation of the clock gene. Our study also confirms the genotypic effect of OXTR rs1042778 on prosociality in complaint situations (i.e., when someone is asked to perform a prosocial behavior), which is in agreement with previous studies, indicating that the GG genotype is associated with high prosociality [15,25].

**Figure 1.** Means and SEMs of Emotional Prosocial Tendencies Measure depending on the interaction of AVPR1b rs28373064 and clock rs6832769. $G^+\!/G^+$: Carriers of the genotype configuration $G^+\!/G^+$, GG or GA for AVPR1b rs28373064 and GG or GA for clock rs6832769; $G^+\!/G^-$: Carriers of GG or GA for AVPR1b rs28373064 and AA for clock rs6832769; $G^-\!/G^+$: Carriers of AA for AVPR1b rs28373064 and GG or GA for clock rs6832769; $G^-\!/G^-$: Carriers of AA for AVPR1b rs28373064 and AA for clock rs6832769.

doi:10.1371/journal.pone.0109086.g001

**Figure 2.** Means and standard deviations of total Prosocial Tendencies Measure depending on the interaction of OXTR rs1042778 and clock rs1801260. $T^+\!/C^+$: Carriers of the genotype configuration $T^+\!/C^+$, GT or TT for OXTR rs1042778 and CT or CC for clock rs1801260; $T^+\!/C^-$: GT or TT for OXTR rs1042778 and TT for clock rs1801260; $T^-\!/C^+$: GG for OXTR rs1042778 and CT or CC for clock rs1801260; $T^-\!/C^-$: GG for OXTR rs1042778 and TT for clock rs1801260.

doi:10.1371/journal.pone.0109086.g002
Because it is central to circadian rhythms, the clock gene determines the biological timing of successful psychological adaption, which partially explains the biological correlates, such as mood and behavior [11]. For example, TT carriers of clock gene rs1801260 tend to be morning types and are more conscientious, agreeable and emotionally stable (confirmed as a prosocial personality) compared with C allele carriers, who tend to be evening types, are more impulsive and express emotional apathy [9]. However, we did not find a direct association between the clock gene and prosociality, although it has been well established that the formation and maintenance of sleep phase timing and diurnal preferences, such as morning/evening preferences, are regulated by the transcriptional activation of the clock gene [7,11]. We propose that the clock gene may affect prosociality [13]. One possible explanation, which is based on the mechanism of CLOCK-BMAL1 heterodimer bindings to E-box enhancers, may be that the clock gene influences prosociality through indirect neurophysiological pathways involving other systems, such as OXT-AVP neural pathways, including OXTR and AVPR1b.

Indeed, our results demonstrated that combinations of clock and OXTR polymorphisms were associated with prosociality. For example, only the group carrying both risk alleles (CC/CT of clock rs1801260 and TT/GT of OXTR rs1042778) reported lower levels of prosociality, whereas those subjects with only one risk allele did not demonstrate these lower levels. The C allele of clock rs1801260 is characterized by an extreme evening inclination and a high risk of bipolar disorder as well as depression [11,29,30]. Additionally, bipolar disorder and depression are closely related to apoptosis and gene rs1801260 is characterized by an extreme evening inclination and a high risk of bipolar disorder as well as depression [11,29,30]. Furthermore, the clock gene regulates mood-related behaviors via a role in dopamine metabolism [33]; dopamine possibly stimulates AVP release in part based on receptor affinities, interacting to facilitate pair-bond formation [36]. Thus, this combination of clock and AVPR1b alleles may affect an individual’s emotional activation levels synchronously, leading to variations in prosocial behavior. Moreover, previous studies have reported many combined effects of circadian clock genes (or components) and other genes (or components). For example, clock gene influences mood by regulating monoamine oxidase A in dopamine metabolism [35] and resistance to weight loss in combination with the sirt1 gene [37]. It appears that the clock gene influences the expressions of other genes through the processes of cell metabolism and extracellular signaling [38], which may represent the underlying mechanism of the effects of the clock gene on social behavior.

In summary, we have provided the first evidence that human prosociality is affected by the combined effects of genetic variations in the clock gene and genes involved in the OXT and AVP systems. A limitation of our study was the small size of the combined group possessing the C allele of clock rs1801260 and the T allele of OXTR rs1042778 (n = 7, 1.6%); it is possible that the C allele frequency of clock rs1801260 is minor, especially within the Asian population (i.e., 9.0% in Han Chinese; 8.3–9.1% in Koreans) [39,11]. The focus on male participants allowed us to avoid potential gender bias in our results [40], but it also limited the generalizability of the present findings. Further replication of these findings in independent study samples (including female subjects) and a meta-analysis to confirm the combined gene effects are needed. Future studies using situational prosocial behavior tasks will be necessary to confirm our results, which were based on self-reported data. The mechanisms underlying the observed associations of these combinations remain to be elucidated. The clock gene may be a point through which changes in cellular energy metabolism influence the functioning of the OXT and AVP systems. Future studies are necessary to determine these mechanisms.

In conclusion, this study demonstrates a link between clock genotypes and prosociality phenotypes, indicating that the combined effects of genetic variations in the clock gene and genes involved in the OXT and AVP systems may contribute to human prosociality. In addition, we provide genetic evidence that further explains the mechanisms underlying prosocial behavior.

### Table 3. Means and standard deviations of Public Prosocial Tendencies Measure depending on the interactions of OXTR rs237887 and clock rs6832769.

| rs6832769 G+ (GGA-GA) | clock rs6832769 G− (AA) |
|-----------------------|-------------------------|
| **OXTR rs237887 A+ (AA+AG)** | **OXTR rs237887 A− (GG)** |
| n (%) | M (SD) | n (%) | M (SD) |
| 138 (32.2%) | 2.99 (0.91) | 165 (38.6%) | 3.13 (0.77) |
| 65 (15.2%) | 3.12 (0.75) | 60 (14.0%) | 2.90 (0.68) |
Supporting Information

Data S1  Data S1 is the raw data of our paper, including the raw data of each dimension of PTM scale, the genotypes of each participant as well as the demographic variables. (SAV)

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