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Research paper

Oxytocin receptor gene variation rs53576 and alcohol abuse in a longitudinal population representative study

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ABSTRACT

Background: Oxytocin is an important regulator of social relationships and has been implicated in development of substance use and addiction. We examined the association of a variance in the oxytocin receptor gene (*OXTR* rs53576 polymorphism) with alcohol use in a population-representative sample, and potential moderation by social functioning.
Methods: The analysis was carried out on the older birth cohort of the longitudinal Estonian Children Personality Behaviour and Health Study (ECPBHS), a cohort of initially 15 years old children (original $n = 593$) recalled at ages 18 and 25. In all data collection waves the participants reported the frequency of consuming alcoholic beverages. Psychiatric interview was carried out at age 25 to assess the lifetime prevalence of substance use disorders. Adverse social interactions with teachers, classmates and family members were self-reported at ages 15 and 18. The minor (A) allele frequency was 0.37.
Results: Males homozygous for the A allele (suggested to be associated with less efficient oxytocinergic functioning) were more frequent alcohol consumers at ages 15 and 18 and also more likely to have had alcohol abuse or addiction by age 25 compared to male G allele carriers. Alcohol use was not associated with the *OXTR* genotype in females. Both male and female AA homozygotes who had reported less favourable relations with their teachers at age 15 more likely had alcohol use disorder.
Conclusions: OXTR rs53576 polymorphism is associated with alcohol use and prevalence of alcohol use disorders in males, and this may be moderated by inferior interpersonal relationships.

1. Introduction

Alcohol consumption is a causal factor in more than 200 disease and injury conditions, causing death and disability relatively early in life: In the age group 20–39 years approximately 25% of the total deaths are alcohol-attributable (WHO, 2014). The chronic and relapsing nature of alcoholism brings about huge economic costs and makes it most urgent to find predictive biomarkers for selection and monitoring a therapeutic course of action, and to help researchers evaluate new therapeutic interventions (Volkow and Baler, 2013).

There is accumulating evidence of an interaction between the neural substrates of affiliative behaviour and those of drug reward, with a role for brain oxytocin systems in modulating acute and long-term drug effects. Oxytocin, a nine amino acid neuropeptide (nonapeptide) is synthesized primarily in the magnocellular neurosecretory cells of the paraventricular and supraoptic nuclei of the hypothalamus and stored in the posterior pituitary gland, but extensive pathways containing oxytocin are present already in teleosts and highly developed mesolimbic tracts exist in mammalians (Grinevich et al., 2016). High density of oxytocin receptors has been found in brain regions involved in regulating mood, social behaviour and addictive processes, such as the central nucleus of amygdala, nucleus accumbens and ventral pallidum (Gimpl and Fahrenholz, 2001). Oxytocin is a potent modulator of a variety of brain functions including learning, memory, emotions, mood, and social and sexual behaviour (reviewed by Sarnyai, 2011). Recent preclinical studies in rodents have reported a remarkable ability of exogenously delivered oxytocin to inhibit stimulant and alcohol self-administration, to alter associated drug-induced changes in dopamine, glutamate and Fos expression in cortical and basal ganglia sites, and to prevent stress- and priming-induced relapse to drug seeking (reviewed by McGregor and Bowen, 2012).

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Intranasal administration of oxytocin has been found to elicit a variety of physiological and behavioural effects in humans, including reduction of anxiety (de Oliveira et al., 2011), and plasma levels of oxytocin-reactive autoantibodies correlate with mood states (Garcia et al., 2011). It has been suggested that anxiety disorders increase the risk for developing alcohol use disorders (Boschloo et al., 2013; Kessler et al., 1997). Oxytocin has been found to enhance functional connectivity between the amygdala and the bilateral insula and middle cingulate/dorsal anterior cingulate gyrus during the processing of fearful stimuli, suggesting that oxytocin may have broad pro-social implications such as enhancing the integration and modulation of social responses especially in anxiogenic contexts (Kirsch et al., 2005; Gorka et al., 2015). By reducing anxiety, increasing the ability to cope with stress, and possibly reversing established alcohol tolerance, oxytocin treatment may diminish craving and facilitate sobriety. Indeed, oxytocin treatment not only blocks alcohol withdrawal in human subjects (Pedersen et al., 2013) but has also been shown to decrease alcohol preference in animals (McGregor and Bowen, 2012). However, these results should be interpreted with caution: it has recently been brought up that studies analyzing the effects of intranasally administered oxytocin are generally underpowered (Walum et al., 2016) and it is unclear what percentage of peripherally administered oxytocin reaches oxytocin receptors in the brain (Leng and Ludwig, 2016).

The human oxytocin receptor gene (*OXTR*) is located on chromosome 3p25, spans about 17 kb, consists of three introns and four exons (Inoue et al., 1994), and encodes a 389-amino acid polypeptide with seven transmembrane domains thus belonging to the class I of the G-protein-coupled receptor family (Gimpl and Fahrenholz, 2001). One of the common polymorphisms (rs53576) in the *OXTR* gene has recently been found to modulate the effect of oxytocin administration (Feng et al., 2015): oxytocin increased the reward or salience of positive social interactions for male major allele (G) homozygotes, while decreasing those processes for female major allele (G) homozygotes. This single nucleotide polymorphism (SNP) of an adenine (A, $f \approx 0.4$) or guanine (G, $f \approx 0.6$) within the third intron (rs53576) appears as a particularly promising marker of inter-individual differences in oxytocinergic function (Tost et al., 2010; Wu et al., 2005). Although the molecular functionality of this SNP is still unknown (Feng et al., 2015), the A allele has been suggested to be associated with less efficient oxytocinergic functioning in experimental settings (Marsh et al., 2012), and this would be theoretically consistent with association studies: the A allele carriers have lower levels of optimism, mastery, and self-esteem (Saphire-Bernstein et al., 2011), lower general sociality (Li et al., 2015), empathy, and higher levels of stress reactivity (Rodrigues et al., 2009). Significantly lower non-verbal intelligence has been found in the A allele homozygotes and lower verbal intelligence on a trend level in A allele carriers (Lucht et al., 2009). Different *OXTR* polymorphisms have been found to moderate the effects of alcohol use on aggressive behaviour in males, suggesting that alcohol has a larger effect on aggressive behaviour for those who, due to altered oxytocin signaling, already in a sober state have more difficulties with social abilities (Johansson et al., 2012a, 2012b; LoParo et al., 2016).

Social skills are highly needed in the school context, and not only for getting along with peers but also in relationships with teachers. Given what has been described for the *OXTR* rs53576, possessing the A allele might carry a higher risk of developing interpersonal problems in adolescence that in turn could lead to worse grades and lower academic competence (Buhs et al., 2006). As the A allele carriers are thought to be less likely to adopt problem-focused strategies in unsupportive interactions (McInnis et al., 2015), they might instead be more prone to start using alcohol to relieve their problems if these emerge.

Table 1
The number of subjects with complete valid data on genotype for the *OXTR* rs53576 polymorphism and other measures by study wave.

Age	15 yr	18 yr	25 yr
Frequency of alcohol use	577	443	539
Lifetime prevalence of AUD	–	–	501
ECPBHS Child Questionnaire			
adverse relations with teachers	578	432	–
relations with classmates	579	426	–
bullying/rejection	581	429	–
Tartu Family Relationships Scale			
Closeness	–	355	–
Support	–	383	–
Misprize	535	390	–
Abuse	–	391	–

Associations of the *OXTR* rs53576 variation in healthy individuals have been found to be gender dependent: Significantly lower local functional connectivity density of the hypothalamus and weaker resting-state functional connectivity between the hypothalamic regions and the left dorsolateral prefrontal cortex have been found in AA homozygotes, but only in males (Wang et al., 2013). Oxytocin has also been reported to increase the reward by or salience of positive social interactions in male GG homozygotes, while decreasing those processes in female GG homozygotes (Feng et al., 2015).

Based on previous findings it can be hypothesized that susceptibility to alcohol abuse is affected by individual differences in the oxytocinergic signal transmission. Hence we aimed at assessing the association of the *OXTR* rs53576 polymorphism with alcohol use and prevalence of alcohol use disorders (AUD) in a population-representative sample. Given that the *OXTR* rs53576 polymorphism has been found to affect coping styles in the face of unsupportive responses from others, we also included relations with teachers, classmates and family members into the analysis, hypothesizing that inefficient social functioning moderates the association between the SNP and alcohol use.

2. Material and methods

2.1. Study population

This analysis was carried out on the older birth cohort of the longitudinal Estonian Children Personality Behaviour and Health Study (ECPBHS), initially a cohort of 15 (recalled at ages 18 and 25) year old children. The rationale and procedure of sample formation have been described elsewhere (Harro et al., 2001). ECPBHS is population representative, while 79% of subjects of the randomized regional sample participated in the original data collection. The total number of subjects in the first wave in 1998/99 was 593 (mean age = 15.4, SD = 0.6). The follow-ups were in 2001 (n = 479, including 62 additional subjects, mean age = 18.4, SD = 0.9) and 2008 (n = 541, mean age = 24.7, SD = 0.7). All the subjects are of Caucasian descent. The number of subjects with valid genotype and psychometric data is given for each analysis separately in Table 1. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu, and written informed consent was obtained from all the participants, and in case of minors, also from their parents.

2.2. Alcohol use

In all data collection waves the participants reported how often they had consumed different types of alcoholic beverages (Merenäkk et al., 2003). Data collection was performed in the uniform conditions of laboratory at each wave. Based on the most