Stressful life events increase aggression and alcohol use in young carriers of the GABRA2 rs279826/rs279858 A-allele

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Abstract
Research of GABRA2 gene in alcohol use and impulse control suggests its role in aggressive behaviour. The purpose of the present study was to examine the effects of GABRA2 genotype and stressful life events on aggressive behaviour, alcohol use frequency and occurrence of alcohol use disorder in a population representative sample of adolescents followed up from third grade to 25 years of age. The sample consisted of the younger cohort of the longitudinal Estonian Children Personality, Behaviour and Health Study. Aggressive behaviour was rated with the activity scale of af Klinteberg, Illinois Bully Scale and Buss-Perry Aggression Questionnaire. Stressful life events and alcohol use were self-reported. Life history of aggression and lifetime occurrence of psychiatric disorders were estimated in a structured interview. The sample was genotyped for GABRA2 rs279826 and rs279858 polymorphisms that are in strong linkage disequilibrium and yielded very similar findings: Higher number of stressful life events reported at age 15 was associated with increased fighting in A-allele carriers, but not in GG homozygotes. At age 25, A-allele carriers exposed to higher stress had consumed alcoholic beverages more frequently at age 15, and by age 25, they had alcohol use disorder with higher prevalence. The results of the present study suggest that the GABRA2 genotype interacts with stress in young people with impact on the development of alcohol use and aggressive behaviour.

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1. Introduction
Gamma-aminobutyric acid (GABA) is the inhibitory neurotransmitter in the brain playing a major role in regulating
neuronal excitability (Olsen and Sieghart, 2009). The fast inhibitory effect of GABA is mediated through GABA type-A (GABA_A) receptors, which are heteropentameric ligand-gated ion channels permeable to chloride (Hevers and Lüddens, 1998). The role of GABA_A receptors in the development of ethanol dependence is well established (Enoch, 2008; Trudell et al., 2014), and the association between increased risk for adult alcohol dependence and various single nucleotide polymorphisms (SNPs) in the GABRA2 gene encoding the α2 subunit of the GABA_A receptor has been found in multiple studies (Covault et al., 2004; Lappalainen et al., 2005; Soykia et al., 2008; Enoch et al., 2009; Li et al., 2014). Research conducted on the GABRA2 gene in impulse control and ethanol use has led investigators to reveal its role in aggression (Simons et al., 2013; Strac et al., 2015), conduct disorder (Dick et al., 2006), and externalizing behaviour problems (Dick et al., 2009; Villafuerte et al., 2014). Indeed, animal studies have strongly implicated the GABA system in the inhibition of aggressive behaviour, administration of positive modulators of GABA_A receptors such as benzodiazepines reliably reducing aggressive behaviours in rodents (Valzelli et al., 1967).

The minor allele of the GABRA2 has been associated with greater disinhibition and excitability in the brain (Edenberg et al., 2004), and past research has reported the G-allele of GABRA2 rs279858 and rs567926 to be associated with increased risk of problem behaviour. The G-allele of GABRA2 rs279858 has been associated with externalizing problems in adolescence (Dick et al., 2009), impulsiveness, and increased response in insula and amygdala during incentive anticipation in fMRI study (Villafuerte et al., 2012). Strac et al. (2015) have reported that in patients with alcohol dependence, the A-C (rs567926 and rs279858) haplotype carriers were more likely to demonstrate aggressive behaviour. However, there are also studies, which have found the major (A) allele of rs279858 and rs279826 to be associated with increased risk for alcohol and drug dependence (Agrawal et al., 2004; Lind et al., 2008), and externalizing behaviour (Dick et al., 2014; Wang et al., 2016).

A few studies examining GABRA2 × environment interaction effect on substance use disorders have been published: one has demonstrated the interaction of childhood trauma with variation of GABRA2 rs11503014 to influence addiction vulnerability: the impact of high childhood adversity on cocaine addiction was apparent in African American males with the 11/12 genotype (Enoch et al., 2010), and another has, paradoxically, reported a protective effect of positive life events for males with the high-risk GABRA2 rs279871 AA genotype from alcohol dependence (Perry et al., 2013). Regarding aggression, in adolescents, a GABRA2 × environment interaction has been found: the association of GABRA2 variants with externalizing behaviour was diminished by high levels of parental monitoring (Dick et al., 2009). According to Villafuerte et al. (2014) subjects with the GABRA2 rs279826 GG genotype were more influenced by delinquent peers compared to A-allele carriers, demonstrating higher levels of externalizing and rule breaking behaviour. While the available evidence has not revealed reproducible gene-environment interactions, it is however highly likely that common genetic variations in the GABRA2 gene predict differences in response to the environment. Adaptive responses to environment encompass regulation of neural circuits underlying anxiety (Panksepp, 1998) and GABA_A receptor-mediated neurotransmission moderates emotional reactions to stimuli and response to stress through actions on the activity of brain limbic structures such as amygdala, but also insula and striatum (Myers et al., 2016). Heightened activation of these structures is also associated with elevated vigilance and emotional reaction to environmental events. Deficiencies in the activation of postsynaptic GABA_A receptors may result in anxiety and increased fear responses (Stephens et al., 1987; Dorow and Duka, 1986), and an increase in GABA levels by GABA transaminase inhibition reduces anxiety (Sherif et al., 1994). The α2 subunit of the GABA_A receptor is particularly important in the modulation of GABA-ergic neurotransmission that controls the anxiety circuits. Humans report drinking alcohol to reduce anxiety (Braun et al., 2012), anxiety often precedes alcohol abuse and anxiety disorders and alcohol use disorder are highly co-morbid.

Taking into account all these previous findings, it appears highly likely that developmental and environmental conditions may interact with the GABRA2 genotype to potentially increase aggressive behaviour and vulnerability to ethanol abuse in adolescents. The purpose of the present study hence was to examine the effects of GABRA2 genotype and stressful life events on aggressive behaviour, alcohol use frequency and occurrence of alcohol use disorders in a population representative sample of adolescents followed up from third grade to 25 years of age. Consistent with the majority of the findings reporting that the minor allele of GABRA2 is associated with genetic risk (Covault et al., 2004; Edenberg et al., 2004; Dick et al., 2009; Villafuerte et al., 2012), we expected a significant GABRA2 × stressful life events interaction, in which stress would have a larger impact on aggressive behaviour and alcohol consumption among participants homozygous for the minor allele (GG genotype) compared to A-carriers across GABRA2 SNPs (rs279826 and rs279858).

2. Experimental procedures

2.1. Participants

The sample consisted of the younger cohort of the European Youth Heart Study conducted in Estonia in 1998/99 which was incorporated into the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS). It is an ethnically homogeneous sample of Caucasian subjects and the rationale and procedure of sample formation has previously been described (Harro et al., 2001). In brief, all schools of Tartu County, Estonia, which agreed to participate (54 of the total of 56) were included into the sampling using the probability proportional to the number of students of the respective age groups in the school, and 25 schools were selected. In 1998/99, all children from grades 3 and 9 were invited to participate and written informed consent was received from 79% of the invited subjects and their parents. Data used in the present analysis were collected during the first, second, third and fourth study wave in 1998, 2004, 2007 and 2014, respectively. The total number of participants in the first study wave at age 9 was 583 (male n=260), and of these subjects 483 (male n=222) participated in the second wave at age 15, 457 (male n=201) in the third wave at age 18, and 441 (male n=193) in the fourth wave at age 25. The participants provided their written informed consent prior participation. In case of minors, also parents signed the consent form.
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