Pharmacology, Biochemistry and Behavior 130 (2015) 59–66

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

A family history of Type 1 alcoholism differentiates alcohol consumption in high cortisol responders to stress

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ARTICLE INFO

Article history:
Received 4 July 2014
Received in revised form 21 November 2014
Accepted 18 December 2014
Available online 24 December 2014

Keywords:
Alcohol
Family history of alcoholism
Stress
TSST
High and low cortisol responders

ABSTRACT

Background: The differentiation between high and low cortisol responders to stress is of interest in determining the risk factors which may, along with genetic vulnerability, influence alcohol intake.
Study 1: Methods: Thirty-two healthy volunteers, family history positive to alcoholism (FHP, n = 16) and family history negative (FHN, n = 16) attended two laboratory sessions during which alcohol or placebo was offered.
Results: There were no differences in consumption of alcohol or placebo between FHP and FHN subjects.
Study 2: Methods: Fifty-eight healthy social drinkers, FHP (n = 27) and FHN (n = 31) attended two laboratory sessions. They were administered either alcohol or placebo in both sessions they attended. All subjects underwent either a stress task (the Trier Social Stress Test, TSST) or a stress-free period, at two separate occasions, before being offered beverage. After the salivary cortisol analysis, subjects in each group were divided into high (HCR) or low (LCR) cortisol responders.
Results: After stress, subjects who were FHP-HCR consumed more alcohol than FHN-HCR. There were no differences in the placebo intake between FHP and FHN subjects regardless of their cortisol response.
Conclusions: This result indicates that stress promotes alcohol consumption only in subjects with a family history of Type 1 alcoholism who show an increase in cortisol response to stress. This behaviour is similar to that previously observed in alcohol dependent individuals after stress and thus could represent an endophenotype posing a risk for future development of alcohol use disorders.

1. Introduction

Consumption of drugs results from a complex interaction between direct drug effects, individual characteristics and the environment. There is a large body of literature providing evidence that a family history of alcoholism influences alcohol use in humans, and fewer studies about which component is affected by a family history. The HPA-axis response to stress has been gaining importance in recent years and a series of clinical studies have investigated stress as a predictor of alcohol abuse in this vulnerable population, demonstrating that stress can trigger not only an increased alcohol intake (Söderpalm Gordh et al., 2011) but also lead to an increased chance of relapse (Adinoff et al., 2005). Activation of the HPA axis releases glucocorticoids which, according to many studies, can sensitize the mesolimbic dopamine (DA) reward system and strengthen the rewarding effects of alcohol (e.g. Piazza and le Moal, 1996).

Activation of the HPA-axis is genetically influenced, and the stress response in one individual remains quite stable over time (Federenko et al., 2004; Bartels et al., 2003). Individual differences in HPA activation thus represent a factor determining vulnerability to addiction, possibly via processes involved in sensitization of the reward system. In preclinical studies, stress-induced HPA-axis activation followed by release of glucocorticoids resulted in increased alcohol consumption, possibly by enhancing mesolimbic DA activation (Marinelli and Piazza, 2002). Further, Piazza and le Moal (1996) showed that acute administration of corticosterone increases DA levels in the nucleus accumbens (NAcc), but only in rats whose DA system was already activated, for example those with higher DA tone or during food intake. In addition, monkeys displaying high cortisol levels of stress during infancy consumed larger amounts of alcohol during adulthood (Fahlke et al., 2000). HPA-axis activation after stress may therefore be a predictor of voluntary alcohol consumption (Prasad and Prasad, 1995).

It is known that subjects with family history positive (FHP) of alcoholism show different levels of sensitivity to the acute effects of alcohol than family history negative (FHN) individuals (Newlin and Thomson, 1990; Schuckit, 1994; Morzorati et al., 2002; Erblich et al.,

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http://dx.doi.org/10.1016/j.pbb.2014.12.008

2003; Conrod et al., 1997), which can make FHP subjects more likely to consume more alcohol. However, studies investigating alcohol's effects on stress-induced HPA-axis response between FHP and FHN non-dependent subjects have shown inconclusive results (Zimmermann et al., 2004; Dai et al., 2002). Zimmermann et al. (2004, 2009) found a higher alcohol-induced dampening of physiological stress response in FHP in comparison to FHN subjects after consumption of 0.6 g/kg alcohol prior to a stress task. Oppositely, an acute dose of 0.5 g/kg of alcohol administered prior to a stress task, dampened HPA-axis activation in FHN but not in FHP subjects (Dai et al., 2007). In other alcohol challenge studies differences in the levels of beta-endorphin (Dai et al., 2005), ACTH and cortisol (Dai et al., 2002) were found between FHP and FHN subjects following stress. Additionally, in a paper by the authors, a significantly higher consumption of alcohol following exposure to an acute stressful situation was observed in FHP subjects in comparison to FHN subjects (Söderpalm Gordh et al., 2011). Taken together, alterations of the stress-induced HPA-axis response to alcohol consumption may contribute to different drinking patterns between FHP and FHN subjects. This raises the question whether altered stress response is of relevance for the development of alcohol related disorders.

In order to determine mechanisms underlying alcohol consumption due to stress we were inspired by Kirschbaum et al. (1995) who found evidence for the existence of high vs. low cortisol responders (HCR vs. LCR) to an acute stress situation. A differentiation between high and low responders to psychosocial stress is of significant interest regarding the pituitary-adrenocortical system (Schommer et al., 2003). Evidence suggests that glucocorticoid low responders might be more prone to, for example, autoimmune disorders, whereas cortisol hyper-reactivity might be more related to vulnerability of infectious diseases (Kirschbaum et al., 1995). Furthermore, high cortisol reactivity to an acute stress task resulted in increased food intake in humans (Epel et al., 2001) supporting the literature linking together networks involved in modulating intake of food and drugs of abuse (Berridge, 1996; Koob and Le Moal, 1997; Kreek and Koob, 1998). This result was supported by that high cortisol responders to an acute stress task had greater BMI and reported greater emotional eating (Tomiyama et al., 2011). In addition, Wand et al. (2007) demonstrated that healthy young adults responding to stress with high cortisol levels were also higher DA responders and experienced positive effects of amphetamine to a higher degree than low cortisol/DA responders.

Individual determinants of alcohol consumption induced by different cortisol response to a stressful situation could help explain why some individuals tend to increase their alcohol consumption, i.e. why some individuals pass the boundary between casual drinking and uncontrolled alcohol consumption, and others do not. Whether healthy FHP-HCR to a stressful situation consume more alcohol than FHP-LCR or FHN-HCR/LCR, has to our knowledge never been investigated. It has been suggested that the development of Type 1 alcoholism requires an interaction between genetics and adverse environmental conditions, which could include stress (Cloninger et al., 1988).

Type 1 alcoholism is the most common form of alcoholism characterized by a late onset of dependence, low prevalence of familial alcoholism and a milder course, in contrast to Type 2, which is characterized by early onset of dependence, high familial alcoholism in fathers, frequent antisocial personality, and the intensity of alcohol-related problems (Cloninger et al., 1988; Babor et al., 1992). Type 1 hereditary is considered to be "milieu-limited", meaning that genetics interact with an unfavourable milieu to inflict increased risk of developing alcoholism, whereas Type 2 heredity appears milieu independent. The development of Type 1 alcoholism seems to be related to adverse environmental conditions e.g. stress, therefore individuals with Type 1 history may be particularly susceptible to alcohol consumption after a stressful situation. In order to assess Type 1 alcoholism in the FHP population, a detailed questionnaire was administered (Söderpalm Gordh and Söderpalm, 2011; see method).

The purpose of the present study was to investigate if individuals that are FHP or FHN for Type 1 alcoholism differ in experimental voluntary alcohol consumption and if there would be an interaction between the stress response (i.e. HCR and LCR) and the heredity (FHP vs. FHN) in this respect.

2. Materials and methods

2.1. Subject recruitment and screening

2.1.1. Study 1

Thirty-two healthy men and women, non-problem social drinkers, between the ages of 19-35 participated. Half of the subjects had a family history of Type 1 alcoholism.

Table 1
Demographics and drug use data of subjects in the FHP and the FHN groups in *Study 1* and in *Study 2*. No significant difference was found between groups in either study.

	Study 1		Study 2	
	FHP (n = 16)	FHN (n = 16)	FHP (n = 27)	FHN (n = 31)
Gender (*n*)				
Female	7	6	12	17
Male	9	10	15	14
Age (*years*, *mean* ± *SEM*)	23.9 ± 0.6	23.3 ± 0.7	25.0 ± 0.6	24.0 ± 0.5
Weight (*kg*, *mean* ± *SEM*)	70.4 ± 3.8	63.0 ± 2.6	71.7 ± 3.2	69.7 ± 1.8
Race/ethnicity (*n*)				
Caucasian	16	16	25	31
Asian	0	0	1	0
Hispanic	0	0	1	0
Current drug use				
Alcoholic drinks (*n/week*, *mean* ± *SEM*)	4.9 ± 0.5	4.8 ± 0.5	5.3 ± 0.6	5.4 ± 0.7
Caffeine consumers (n users)	7	12	14	19
Cups of coffee (n/day)	1	1.5	1	1
Cigarettes consumers on daily basis (n users)	1	0	0	1
Cigarettes consumed (n/day)	3	0	0	2
Lifetime drug use (*n ever used*)				
Stimulants	0	0	1	4
Tranquilizers	0	0	1	1
Hallucinogens	0	0	0	0
Opiates	1	0	0	0
Marijuana	7	5	14	9