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# Sex hormone activity in alcohol addiction: Integrating organizational and activational effects

Bernd Lenz [a,*], Christian P. Müller [a], Christina Stoessel [a], Wolfgang Sperling [a], Teresa Biermann [a], Thomas Hillemacher [b], Stefan Bleich [b], Johannes Kornhuber [a]

[a] Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Germany
[b] Center for Addiction Research (CARe), Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Germany

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ABSTRACT

There are well-known sex differences in the epidemiology and etiopathology of alcohol dependence. Male gender is a crucial risk factor for the onset of alcohol addiction. A directly modifying role of testosterone in alcohol addiction-related behavior is well established.

Sex hormones exert both permanent (organizational) and transient (activational) effects on the human brain. The sensitive period for these effects lasts throughout life. In this article, we present a novel early sex hormone activity model of alcohol addiction. We propose that early exposure to sex hormones triggers structural (organizational) neuroadaptations. These neuroadaptations affect cellular and behavioral responses to adult sex hormones, sensitize the brain's reward system to the reinforcing properties of alcohol and modulate alcohol addictive behavior later in life. This review outlines clinical findings related to the early sex hormone activity model of alcohol addiction (handedness, the second-to-fourth-finger length ratio, and the androgen receptor and aromatase) and includes clinical and preclinical literature regarding the activational effects of sex hormones in alcohol drinking behavior. Furthermore, we discuss the role of the hypothalamic-pituitary-adrenal and -gonadal axes and the opioid system in mediating the relationship between sex hormone activity and alcohol dependence.

We conclude that a combination of exposure to sex hormones *in utero* and during early development contributes to the risk of alcohol addiction later in life. The early sex hormone activity model of alcohol addiction may prove to be a valuable tool in the development of preventive and therapeutic strategies.


**Contents**



*Abbreviations:* AAS, anabolic-androgenic steroids; ACTH, adrenal corticotropin hormone; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; AMS, antenatal maternal stress; AR, androgen receptor; BMI, body mass index; CA1, Cornu Ammonis area 1; COMT, catechol-O-methyltransferase; CRH, corticotropin-releasing hormone; DA, dopamine; 5-DHEA, 5-dehydroepiandrosterone; DHT, dihydrotestosterone; EGCG, epigallocatechin gallate; ESR, estrogen receptor; FAS, fetal alcohol syndrome; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; NO, nitric oxide; OCDS, obsessive compulsive drinking scale; PMS, premenstrual syndrome; POMC, pro-opiomelanocortin; PR, progesterone receptor; SERM, selective estrogen receptor modulator; SHBG, sex hormone binding globulin; SN, substantia nigra; SRD5A1/2, 5-α reductase 1/2; VTA, ventral tegmental area; 2D:4D ratio, second-to-fourth-finger length ratio; 2D:4Dr-l, difference in 2D:4D ratios between the right and the left hands.

* Corresponding author at: Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Schwabachanlage 6-10, D-91054 Erlangen, Germany. Tel.: +49 913 1853 3001; fax: +49 913 1853 4105.
*E-mail address:* bernd.lenz@uk-erlangen.de (B. Lenz).

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## 1. Introduction

Alcohol addiction is characterized by a high degree of clinical heterogeneity, which is based on an even greater diversity of the involved neurocircuitries and neuronal systems. Until today, it is not possible to relate unique molecular pathomechanisms to individual patients. However, this goal remains important and carries implications for the development of a successful, individualized treatment algorithm.

The bio-psycho-social model of alcohol dependence suggests that its establishment and manifestation is controlled by a complex interaction of genetics, neurobiology, physiology, and social and environmental characteristics (e.g., chronic stress, lack of control over the putative stressors, degree of coping ability and availability of social support) (Cloninger et al., 1981; Devor and Cloninger, 1989; Knopik et al., 2004; Merikangas et al., 1998; Merikangas and Avenevoli, 2000; Witt, 2007). The subtle balance of risk and protective factors determines whether an individual develops alcohol addiction.

By the 1970s, studies had shown that the brain is a target tissue for steroidal regulation, indicating a potential role of sex hormone activity in the pathophysiology of psychiatric diseases (Stumpf and Sar, 1976). There is robust evidence for sex differences in the epidemiology, etiopathology and course of alcohol dependence. This includes the initiation and escalation of the disease, withdrawal, relapse and treatment. With the exception of testosterone, however, the role of sex hormone activity in alcohol addiction has received surprisingly little attention given the close relationship between alcohol-related behavior and the psychological traits that are controlled by sex hormones, such as impulsiveness, aggression (Archer, 1991; Eriksson et al., 2003; von der Pahlen et al., 2002), antisocial behavior/personality (Buydens-Branchey et al., 1989; Dabbs and Morris, 1990; Moeller and Dougherty, 2001), sensation seeking (Zuckermann et al., 1980), harm avoidance and depression (Berner et al., 1986). Our recent clinical association studies identified links between both alcohol dependence and addictive behaviors and traits such as handedness (Sperling et al., 2000, 2010), the second-to-fourth-finger length ratio (2D:4D ratio) (Kornhuber et al., 2011), and genetic polymorphisms of the androgen receptor (AR) (Lenz et al., 2009, 2010) and the enzyme aromatase (CYP19A1) (Lenz et al., 2011a). These characteristics are associated with both prenatal and lifetime sex hormone exposure, suggesting a common pathophysiological mechanism. Sex hormone activity strongly influences an individual's behavior and the constitution of the brain (Arnold and Breedlove, 1985; Arnold, 2009). Moreover, sex hormones play important roles in the differentiation of behavioral responses to alcohol. At present, it is not clear to what extent sex hormone-induced permanent (organizational) and transient (activational) effects, and the complex interaction of these effects, contribute to one's vulnerability to alcohol addiction.

In this article, we review the literature regarding the role of sex hormones in human alcohol dependence, including findings from animal and cell-based models. In addition, we integrate the early sex hormone activity model and introduce a novel perspective for future alcohol addiction research. We argue that the organizational effects of sex hormones sensitize the cerebral reward system to the reinforcing properties of alcohol. Because considerable pharmacological and non-pharmacological strategies already exist, this area of research has implications for the development of future preventive and therapeutic strategies.

## 2. Sex differences in alcohol drinking and related effects

Pathological alcohol use is a devastating public health issue. Alcohol consumption is one of the leading preventable causes of death worldwide. The recent "Global Status Report on Alcohol and Health" published by the World Health Organization (2011) states that the use of alcohol is responsible for approximately 2.5 million deaths per year. The consequences of alcohol dependence do not exclusively concern the individual, but through the high costs required to treat alcohol-induced disorders, such as