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Review

Sex differences in addictive disorders

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ABSTRACT

Gender-dependent differences in the rate of initiation and frequency of misuse of addicting drugs have been widely described. Yet, men and women also differ in their propensity to become addicted to other rewarding stimuli (e.g., sex, food) or activities (e.g., gambling, exercising). The goal of the present review is to summarize current evidence for gender differences not only in drug addiction, but also in other forms of addictive behaviours. Thus, we first reviewed studies showing gender-dependent differences in drug addiction, food addiction, compulsive sexual activity, pathological gambling, Internet addiction and physical exercise addiction. Potential risk factors and underlying brain mechanisms are also examined, with particular emphasis given to the role of sex hormones in modulating addictive behaviours. Investigations on factors allowing the pursuit of non-drug rewards to become pathological in men and women are crucial for designing gender-appropriate treatments of both substance and non-substance addictions.

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1. Introduction

The term "addiction" is traditionally linked to the abuse of legal and illegal substances. Most drugs of abuse affect the brain reward system thus leading to addiction. However, engaging in non-drug related activities, especially those involving 'natural' rewards, could also activate the reward system and result in addiction. Non-drug addictive behaviours are receiving increased attention from clinicians due to the increasing number of subjects reporting symptoms consistent with impairment of impulse control.

Definition of "behavioural addictions" has been recently expanded to encompass any behaviour characterized by (i) a feeling of tension or arousal before the action, (ii) gratification and/or relief at the time of executing the act, (iii) an inability to resist an urge or drive even against great obstacles or dangers, and (iv) the absence of consideration for the negative consequences that may affect family, friends, or work. As such, behavioural addictions include compulsive food intake and sexual activity, pathological gambling and Internet addiction, excessive exercising, compulsive buying and pyromania. These behaviours, often referred to as "impulse control disorders" or "impulsive–compulsive behaviours", result in actions that are harmful to oneself or to others, and share common features such as compulsiveness, impulsivity, impaired decision-making, craving, tolerance, withdrawal and high rates of relapse. Many of these activities are daily customs contributing to our ultimate survival, and it is therefore not surprising to find some controversy in diagnosing and treating these conditions.

Nowadays, behavioural addictions are increasingly documented worldwide. In the United States, for example, prevalence rates of these disorders have been estimated at 1–2% for pathological gambling (Welte et al., 2001), 5% for compulsive sexual behaviour (Schaffer and Zimmerman, 1990), and 5–6% for compulsive buying (Black, 2007). Notably, behavioural addictions often display neurobiological and neuroanatomical similarities between natural and drug reward processing. In humans, neuroimaging studies have demonstrated that gambling (Breiter et al., 2001), playing video games (Koepp et al., 1998; Hoeft et al., 2008) or shopping (Knutson et al., 2007) activate some of those brain regions (i.e. the mesocorticolimbic system and extended amygdala) activated by drugs of abuse (Volkow et al., 2004). Thus, drug- and food-related cues not only activate common neuroanatomical substrates, but also result in similar activity-regulated gene expression patterns within these brain areas (Kelley et al., 2005). Individuals with decreased serotonergic and/or dopaminergic receptors, and an augmented rate of synaptic dopamine catabolism, appear to

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be predisposed to use any substance and/or to engage in any behaviour that increases dopamine release (Blum et al., 2011). Additionally, compelling evidence demonstrated that non-drug addictions can alter neural plasticity in brain regions that are affected by drugs of abuse, and lead to neuroadaptations similar to those reported after long-term drug use (for a recent review see Olsen, 2011).

Men and women display different attitudes and skills, experience dissimilar emotions in response to environmental and social stimuli, and show diverse susceptibility to stress, illnesses and mental diseases. In this scenario, while a growing number of studies are now paying more attention to evaluate sex-dependent differences in drug addiction, only few studies have examined potential differences between men and women in non-substance behavioural addictions, an issue that only recently is gaining relevance. For example, in a study using multidimensional self-report to measure addictive behaviours, men scored higher than women in exercising, gambling, and having sex, while women scored higher on compulsive shopping and food binging (MacLaren and Best, 2010). The paucity of studies on gender differences in behavioural addictions is particularly surprising when considering the modulatory role of estradiol in effort-based decision making (Uban et al., 2012), its interplay with dopamine in modulating reward and cognitive processes (Becker, 1999; Jacobs and D'Esposito, 2011), and the presence of estrogen receptors within key brain regions implicated in motivation, reward and cost/benefit decision making (Shughrue et al., 1997).

In this review, we summarized the data currently available on sex-dependent differences in drug and non-drug addictions from epidemiology to neurobiology and potential risks factors. Emphasis is given to the more recently identified types of behavioural addictions, such as pathological gambling or Internet addiction, and to the role that sex hormones are likely to play in determining gender differences. However, it should be kept in mind that behavioural addictions always comprise complex interactions between a substance (more or less addictive) or an activity (more or less rewarding), an individual (more or less vulnerable) and an environment (more or less tolerating).

2. Drug addiction

2.1. Gender differences in drug addiction

The brain reward system reinforces behaviours required for species survival, including sex, eating and social interactions. Drugs of abuse co-opt these neural pathways and subjugate normal reward-related behaviour, from which ensue uncontrollable drug seeking and taking. Drug addiction develops after repeated substance use and typically includes a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, and greater importance to obtain the drug than to other goals or activities.

Men and women abuse the same drugs, but not always in the same ways (UNODC, 2013). Significant gender differences have been reported in the initiation of drug use, reasons for continuing to use the drug as well as in the resumption of drug taking after periods of abstinence (relapse), which remains an unmet clinical need for addiction. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), women are more likely than men to abuse prescribed drugs, like tranquilizers and sedatives, while men are more likely to abuse illicit drugs, such as cocaine and heroin (EMCDDA, 2005). Yet, preclinical data revealed usually higher responsiveness to drugs in females than in males. For almost all drugs of abuse, enhanced vulnerability of females to develop drug addiction has been widely recognized, although some discrepancies have been also reported. Evidence from both preclinical and clinical studies have been recently reviewed for cocaine (Quinones-Jenab and Jenab, 2012), amphetamine (Vansickel et al., 2010), opioids (Dahan et al., 2008), nicotine (Pogun and Yararbas, 2009), alcohol (Witt, 2007), phencyclidine (Carroll et al., 2005) and cannabinoids (Fattore et al., 2009) and, therefore, will not be reviewed here.

Both intrinsic sex differences in brain organization and activational effects of circulating gonadal hormones have been proposed to account for the observed sex-dependent differences (Lancaster, 1994; Becker et al., 2001; Hu et al., 2004). Enhancing effects of estrogen, and attenuating effects of progesterone, on drug-induced reward have been consistently reported (Quinones-Jenab and Jenab, 2010; Anker and Carroll, 2011). Similarly, interactions of estrogen with endogenous opioid peptides (Segarra et al., 2010) and the HPA axis (Carroll and Anker, 2010) as well as with dopaminergic neurotransmission (Thompson and Moss, 1994; Becker, 1999; Jacobs and D'Esposito, 2011) have been proposed as mechanisms underlying estrogen facilitative effects. Notably, recent findings indicate that estrogen sensitivity of the different aspects involved in drug-taking behaviour is not uniformly organized, but rather regulated independently during development (Perry et al., 2013). That is, pubertal estradiol affects at a greater extent motivational rather that learning/acquisition processes. The hormonal status associated with the menstrual cycle has been shown to play an important role in drug addiction treatment outcomes in women. Accordingly, the severity of withdrawal symptoms may be greatly different in the luteal and follicular phase of the menstrual cycle (Sofuoglu et al., 1999; Snively et al., 2000; Terner and de Wit, 2006; Allen et al., 2010). Yet, human literature examining the role of estrogen and menstrual cycle on subjective drug effects is still limited. Other factors, however, have been proposed to take part in the propensity to abuse drugs, among which pharmacokinetic, pharmacodynamic, and sociocultural differences (Fattore et al., 2008; Franconi et al., 2012), along with a different sensitivity to aversive properties of drugs (Hashimoto and Wiren, 2008). Discussion of historical, cultural, social and biological bases for sex differences in drug addiction is beyond the scope of this review, as all of the above issues have been systematically reviewed recently by Becker et al. (2012). Indeed, they elegantly collected current evidence on brain neurotransmitter systems and neural circuitries likely contributing to sex differences in drug abuse and dependence.

2.2. Underlying reasons for sex and gender differences in drug addiction

The biopsychosocial model of drug addiction proposes that this psychiatric disorder is regulated by complex interaction of genetic (e.g. sex differences, ethnicity) and environmental factors (e.g. sociocultural diversity, socioeconomic status, stress coping ability). As a result, this model encompasses various facets of individuals, including environment as being either a protective or risk factor. This model also suggests that individual vulnerability may explain the initiation to drug use, which itself results from biological and psychosocial factors. The fine balance between risk and protective factors will then confer/determine whether or not an individual will become addicted to drugs.

2.2.1. Sociocultural and biological differences

Sociocultural and biological perspectives, when combined, might provide satisfactory explanation for sex/gender differences in drug addiction.

On one hand, the sociocultural perspective holds that traditional stigmatization of drug addicts might be a protective factor for women. In fact, tighter cultural constraints are usually placed

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