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Invited review

Psychobiology of cocaine addiction: Contribution of a multi-symptomatic animal model of loss of control

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ABSTRACT

Transition to addiction is the shift from controlled to uncontrolled drug use that occurs after prolonged drug intake in a limited number of drug users. A major challenge of addiction research in recent years has been to develop models for studying this pathological transition. Toward this goal, a DSM-IV/5-based multi-symptomatic model of cocaine addiction has been developed in the rat. It is based on an operational translation of the main features of the disease. 1. Addiction is not just taking drug; it is a non-adaptive drug use: The procedure models addiction in relation to its clinical definition. 2. All drug users do not face the same individual risk of developing addiction: The model includes an individual-based approach. 3. Addiction develops after protracted periods of controlled drug use: This procedure allows for the study of the long-term shift from controlled drug use to addiction.

We describe this model in detail and show how it can contribute to our understanding of the pathophysiology of cocaine addiction.

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1. Introduction

Drug addiction is one of the most prevalent neuropsychiatric diseases afflicting society today. The socio-medical burden is enormous, accounting for approx. 12% of deaths worldwide (WHO, 2013a). As a mental disease (Leshner, 1997), it is complex and multi-faceted, associated with dysfunctions in motivational, emotional, learning and behavioural control systems of the brain (Goldstein and Volkow, 2011; Haney, 2009; Hyman et al., 2006). Thus, it is not surprising that its pathogenesis is poorly understood and treatment possibilities are inadequate.

Drug addiction is a chronic relapsing disorder characterised by loss of control over drug seeking and drug taking, and maintained drug use despite adverse consequences (APA, 2000). It occurs mainly after prolonged drug use and in 20–40% of users, depending on the drug (Anthony et al., 1994; Nutt et al., 2007).

A current triadic model proposes that the pathophysiology of addiction involves interactions between the drug, the environment and a vulnerable phenotype or personality (Kreek et al., 2002). A less vague, older dyadic model (Ausubel, 1961) combined *predisposing factors*, i.e. hereditary or acquired susceptibility, and *precipitating factors*, i.e. drug and environment (drug availability, community or societal tolerance, peer and family domains…). This last model proposed vulnerability through predisposition and introduced a dual, almost functional, dissociation of individual-related factors and external factors that placed the individual at the core of vulnerability.

Despite almost five decades of experimental research, effective treatments are limited, especially for psychostimulant addiction (Kreek et al., 2002). Does this mean that preclinical approaches are in vain? On the contrary, the complexity of this psychopathology is difficult to access in humans, suggesting that preclinical models can play a pivotal role in deciphering the pathophysiology of addiction. Notably, animal models provide valuable ways to investigate the different stages of the drug addiction cycle.

In addition to its inherent individual risk, addiction is indeed a multi-step disease. It is therefore critical to identify which phase is being studied. Another possible confounding factor is that addiction is a multi-faceted disease. Although a unitary view governs the current clinical definitions and theories of addiction, the addict population can be heterogeneous, suggesting distinct pathophysiologies or aetiologies. Last, but not least, addiction is not merely drug use or increased drug use. It is clear from the clinical definition that behavioural differences between drug users and addicts might be best revealed in challenging conditions: in order to obtain drugs, addicts are willing to overcome barriers that users are not.

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In a general theory of transition to addiction (Piazza and Deroche-Gamonet, 2013), we postulate that this pathological process results from sequential interacting influences between the degree of individual vulnerability and the degree of exposure to drugs. We propose that transition to addiction follows a three-step sequence with distinct influences of individual vulnerability and drug exposure: 1. *Sporadic-Recreational drug use*, mediated by the "pleasurable" effects of drugs and occurring in most individuals; 2. *Intensified-Sustained-Escalated drug use*, during which drug intake intensifies, escalates and becomes stably sustained, triggered in few vulnerable subjects by quantitative differences in activity of the brain reward-related system, and maintained by an allostatic state; 3. *Loss of control of drug use and full addiction*, mediated by qualitative changes in the brain reward-related system, manifested in few vulnerable subjects (Kasanetz et al., 2013, 2010).

In this review, we present a multi-symptomatic model, which models transition to the third phase, i.e. loss of control of drug use, developed on the basis of an operational approach. We provide a detailed description of this DSM-IV/5-based model in the rat which, we believe, can contribute to our understanding of the pathophysiology of cocaine addiction (Deroche-Gamonet et al., 2004). We also describe psychobiological data from this model, and advocate for a systematic strategy to explore the psychobiology of addiction.

First, to support the need for – and the possibility of – a new experimental approach of addiction, we present key points that emphasize the underestimated complexity of this pathology.

1.1. Addiction is a multi-step pathology

We know from its natural history (Vaillant and Hiller-Sturmhofel, 1996; Vaillant, 1995), that the pathology progresses from use to addiction through progressive deregulations of use (Kreek et al., 2002).

As mentioned above, we have recently argued that transition to addiction results from a progressive evolution between three consecutive, but independent, phases: 1. *Recreational Sporadic (ReS) drug use*; 2. *Intensive, Sustained, Escalated (ISuE) drug use*; 3. *Loss of Control (LoC) of drug use*, leading to full addiction (Piazza and Deroche-Gamonet, 2013). At this third stage, attempts to quit are mostly unsuccessful and addiction becomes a chronic relapsing disorder.

The three phases are consecutive: entering into one phase is necessary to shift to the next one. They are independent: entering into one phase is not sufficient to get to the next one. The progression between phases is mediated by at least two vulnerable phenotypes (Piazza and Deroche-Gamonet, 2013). A *drug escalation-prone* phenotype would promote the shift to phase 2, inducing the first moderate pathological state. Reaching this *ISuE* phase sets the conditions for addiction to develop as full addiction appears only after a prolonged period of sustained drug use (Deroche-Gamonet et al., 2004). However, a second, *loss of Control-prone*, phenotype is necessary for transition to the third phase, as full addiction only appears in a limited % of individuals showing *ISuE* drug use.

Supporting the view that vulnerability to addiction could be specific and distinct from vulnerability to use (Deroche-Gamonet and Piazza, 2010), some personality traits and psychiatric disorders are more specifically associated with either vulnerability to use (Franques et al., 2000; Sher et al., 2000; Terracciano et al., 2008; Zuckerman, 1986) or addiction (Swendsen and Le Moal, 2011; Swendsen et al., 2010).

Different factors and mechanisms of vulnerability could even be involved within the same stage of pathology. This is particularly easy to conceive for relapse. Different relapse-inducing factors have been identified, i.e. stress, drug-associated conditioned stimuli and small amounts of drug (Childress et al., 1988; Goeders, 2003; O'Brien et al., 1992). Preclinical models of relapse, i.e. reinstatement models, demonstrate involvement of distinct neurobiological mechanisms for the three types of factors, providing several sources for mechanisms of vulnerability (Lê and Shaham, 2002; Shaham et al., 2003; Shalev et al., 2002).

Finally, the same kind of factors could exert a distinct influence on different stages of the disease. There is compelling evidence that environmental factors highly influence the effects of drugs of abuse and could play a critical role in transition to addiction (Batts et al., 2005; Swadi, 1999). However, the term environment is often used confusingly. In this context, the Ausubel's dyadic model for the aetiology of addiction (Ausubel, 1961) distinguishes environmental factors contributing to individual predisposition (acquired susceptibility) from those acting as precipitating factors. In the former, environmental influences are exercised at critical developmental phases (perinatal, adolescence) and may alter one's personality and psychobiological construction so that they become more vulnerable to use or abuse drugs (Khantzian, 1986). In the latter, environmental conditions can refer to drug availability, community or societal tolerance, peer and family domains…, i.e. life context. Accordingly, positive family relationships, friendships, and involvement and attachment appear to protect against the development of drug addiction (Jessor et al., 1980). It remains to be proven that the two types of environmental conditions have the same kind of influence (Piazza and Le Moal, 1996; Somaini et al., 2011).

The role of animal models is pivotal in the understanding of the dynamics of the pathological process. They theoretically provide unique ways to investigate the different stages of the drug addiction cycle.

1.2. Addiction is a multi-faceted disease

Addiction (or dependence) is mainly diagnosed using DSM (APA, 2000) or ICD (WHO, 2013b) classifications which combine several behavioural and pharmacological criteria. A positive diagnosis is given when a given number of criteria are fulfilled, independent of their nature. In addition, classifications are categorical, i.e. a criterion is positive when present, independent of its intensity.

Therefore, addicts do not necessarily show the same clinical table. This is especially true for addicts of different drug classes; cocaine addicts show mainly behavioural criteria whereas heroin and alcohol addicts also show pharmacological symptoms. Critically, the DSM/ICD categorical diagnosis did not capture the dimensional nature of addiction; addicts can differ by the severity of the pathology, even for the same drug (the new DSM 5 released in May 2013 partially corrects this weakness). Addicts can indeed be assigned a severity score (ASI) (McLellan et al., 2006) based on the number of addiction criteria they met, psychiatric comorbidity, and drug-induced social impairments. Inter-individual differences are reflected by differential combinations of symptoms within the same diagnosis, and/or in differential severity of the disease, which might result from distinct physiopathology or aetiology.

Data support the view that the addict population is heterogeneous. Several distinct personality traits, including sensation seeking, anxiety, and impulsivity, are associated with addiction (Ball et al., 1998; Clapper et al., 1994; Conway et al., 2002; Franques et al., 2000; Gossop, 1978; Greene et al., 1993; Labouvie and McGee, 1986; Schinka et al., 1994; Terracciano et al., 2008; Zuckerman, 1986), as well as several distinct comorbid psychiatric disorders (Kessler et al., 1996; Khantzian, 1986; Skinstad and Swain, 2001) and behavioural or cognitive deficits (Bechara, 2005; Cunha et al., 2011; Ersche et al., 2013; Gorodetzky et al., 2011; Verdejo-García et al., 2006, 2007).