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Review article

Reconsidering depression as a risk factor for substance use disorder: Insights from rodent models

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ABSTRACT

Depression and substance use disorder (SUD) often co-exist and are typically associated with an inaccurate diagnosis, worsened clinical course and poor medication adherence compared to either disorder alone. To date, the biological mechanisms contributing to their strong association remain largely unknown. In this review, we critically analyze preclinical literature on psychostimulant drugs and reconsider the common view that depression is a risk factor for drug use and the development of SUD. Unexpectedly, this investigation led us to conclude that depressive-like states in rodents are associated with a low predisposition to drug intake, at least when considering initial, voluntary and regulated psychostimulant intake. We identified several conceptual gaps and methodological challenges potentially misleading when modeling depression and SUD comorbidity. On the basis of these observations, we propose new innovative perspectives to guide future experiments and advance our knowledge in this field, including the use of newly refined rodent models that better capture hallmarks of depression and SUD.

1. Introduction

Co-occurrence of two or more psychiatric diagnoses in the same individual is common in psychiatry (Degenhardt et al., 2003). This form of comorbidity encompasses a wide range of mental health disorders including schizophrenia, mood and anxiety disorders as well as substance use disorder (SUD).

Major depressive disorder (hereafter referred to as depression) is one of the most common psychiatric disorders worldwide despite estimates of its lifetime prevalence varying substantially across countries (Kessler and Bromet, 2013). Depression is characterized by a long-lasting and recurrent depressed mood and/or anhedonia referring to a diminished interest or pleasure in most activities (Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), American Psychiatric Association, 2013). These core symptoms are accompanied by additional symptoms including sleep disturbances, feelings of worthlessness or suicidal ideation. Depression is also accompanied by multiple comorbidities, among which substance use and SUD are particularly common. SUD is characterized by patterns of escalated and sustained drug intake, loss of control over drug intake, and drug craving (DSM-5, American Psychiatric Association, 2013). SUD occurs only in individuals whose drug use opportunities develop into a maladaptive pattern of drug taking and seeking (Lopez-Quintero et al., 2011; Wagner and Anthony, 2002).

Large scale epidemiological studies document strong associations between drug use, SUD and mental health disorders. For instance, prevalence rates of SUD are almost twice as high among individuals with severe depression compared to the general population (Conway et al., 2006; Grant et al., 2016; Swendsen et al., 2010; for review Tolliver and Anton, 2015). Concordantly, depression is 3–4 times more prevalent among individuals diagnosed with SUD than those without SUD (Lai et al., 2015). This reciprocal comorbidity has been observed for all pharmacological classes of addictive drugs, including nicotine, alcohol, cannabis, opiates and psychostimulants (Conway et al., 2006; Grant et al., 2016; Grant et al., 2004; Regier et al., 1990).

2. Depression and substance use disorder comorbidity: why does it occur and matter?

Co-occurrence of depression and SUD in patients who present dual diagnoses has long been recognized as an important consideration in clinical practice. Comorbid depression and SUD is typically associated with an inaccurate diagnosis, worsened clinical course, greater functional impairment, and lower medication adherence compared to either disorder alone (Abou-Saleh, 2004; Merikangas and Kalaydjian, 2007). In addition, mental health and SUD treatment professionals are

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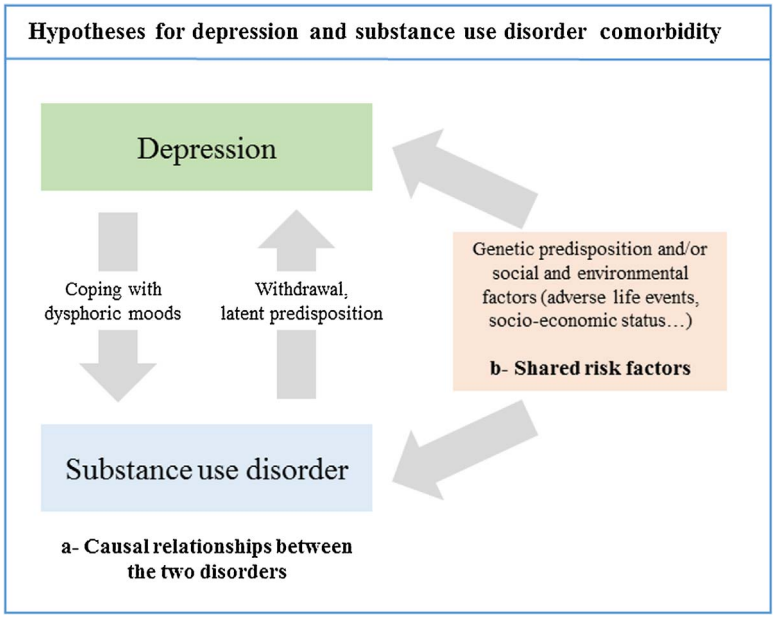

Fig. 1. Hypotheses concerning the reasons why comorbidity of depression and substance use disorder might occur: (a) There are causal relationships between the two disorders: substances are used to relieve dysphoric moods and/or substance use induces or reveals a latent predisposition towards depression; (b) Common risk factors promote the concurrent development of depression and substance use disorder.

confronted with the difficulties of providing effective care to patients whose problems overlap two health care specialties.

Several hypotheses have been proposed to explain the high prevalence rate of comorbid mental health disorders (Degenhardt et al., 2003). Comorbidity can be explained in causal terms, the presence of one disorder increasing the likelihood of another to occur (Fig. 1a). For example, comorbidity may manifest in individuals who use substances and their specific psychotropic effects to cope with emotional distress and reduce dysphoric symptoms associated with depression (Kessler, 2004; Khantzian 1985, 1997; Swendsen et al., 2010) (Fig. 1a). In this type of case, treating the underlying depression would have certain benefits for treating SUD. However, only a small number of double-blind, placebo-controlled trials have been conducted in substance use-dependent patients with depression in order to evaluate the therapeutic impact of antidepressant pharmacotherapy. Several clinical trials have demonstrated a beneficial effect of antidepressants on mood symptoms in patients with comorbid SUD but yet failed to establish their effectiveness on substance use outcomes due to inconsistent results (see Lalanne et al., 2016; Nunes and Levin, 2004; Pettinati et al., 2013). Conversely, substance-induced depression can be observed during acute intoxication and withdrawal from drugs in individuals with SUD (Gawin and Kleber, 1986; Markou and Kenny, 2002). In these patients, symptoms of depression typically disappear within a month or less after abstinence, particularly for those in addiction-treatment settings (Brown and Schuckit, 1988; Nunes and Levin, 2004; Nunes et al., 2004). Comorbidity could also be caused by substance use revealing a latent predisposition toward depression in high-risk individuals which facilitates the expression of depression symptoms (American Psychiatric Association, 2013). Both pathways contribute significantly to the rates of comorbidity between depression and SUD (Schuckit, 2006). Finally, shared predisposing factors such as biological, social or environmental factors may increase the likelihood of depression and SUD explaining their association (Kendler et al., 2003) (Fig. 1b). For example, exposure to early adverse life events in the form of child abuse and/or neglect is a risk factor for both depression and SUD in adulthood and might account for some comorbidity (Gerra et al., 2009; Kessler, 1997; Nemeroff, 2016).

All these scenarios probably contribute, in various degrees, to how and why depression and SUD comorbidities occur, each with different implications for prevention, treatment and future research.

3. Scope of the review: reevaluating depression as a risk factor for psychostimulant intake in rodents

In humans, efforts to understand whether depression precedes and influences drug use and the development of SUD have been hampered by both the difficulties in establishing the sequence of disorder onset and the complex nature of comorbidity in individuals with co-existing psychiatric disorders such as anxiety disorders (Gorman, 1996; Merikangas et al., 1998) and polysubstance use and abuse (Connor et al., 2014).

Animal models, especially rodents, have improved comprehension of the potential risk factors for depression and drug use, and the mutual interactions between these two disorders. These studies have been evaluated in recent comprehensive reviews (see Bardo et al., 2013; Filip et al., 2013; Neisewander et al., 2012; Ng et al., 2016; Paterson and Markou, 2007; Renoir et al., 2012). In particular, converging evidence highlights an enhanced vulnerability to drug use in rodents subjected to social and environmental factors that produce depressive-like behaviors (reviewed in Bardo et al., 2013; Neisewander et al., 2012; Ng et al., 2016). However, regarding depression *per se* as a contributing factor to drug vulnerability, few studies have focused on the complexity of depression and SUD in terms of heterogeneous symptoms, inter-individual variability or diversity of etiological factors. Consequently, there is little evidence from rodent models showing depression as a risk factor for drug use and SUD and many questions and controversies remain unaddressed (Bardo et al., 2013; Filip et al., 2013; Neisewander et al., 2012; Ng et al., 2016).

We therefore reviewed preclinical literature to highlight any inconsistencies and further interpret the data. We applied a focused approach by only analyzing psychostimulant drugs, including amphetamine, cocaine and methamphetamine, in animal models of depression, rather than systematically compiling and comparing literature on drugs of various pharmacological classes. We also critically analyzed the advantages and drawbacks associated with rodent models of depression as well as the design of experimental procedures used to study different aspects of SUD. This highlighted some important methodological and conceptual issues which potentially mislead the modeling of depression