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Review

Drug withdrawal-induced depression: Serotonergic and plasticity changes in animal models

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ABSTRACT

This review discusses recent research of mood disorders associated with the cessation of psychoactive substances, with an emphasis on preclinical studies that have been published in the last decade. Animal models exhibiting anhedonic and depressive-like behaviours associated with drug withdrawal have been used to study the neurobiology of mood disorders and have culminated in the identification of novel targets for the treatment of depressive-like symptoms. This review will introduce the behavioural as well as the neurochemical and plasticity changes in depressed patients and several animal models of depression. Following, we provide a more in-depth discussion of the role of serotonergic neurotransmission and Hypothalamic-Pituitary-Adrenal (HPA) axis regulation as well as the neurogenic changes occurring after chronic drug intake focusing on the withdrawal associated depression. Although we mainly focus on animal data, some relevant human studies are also discussed. Establishing the commonalities of depression and drug-seeking behaviour will allow us to elucidate the factors driving the high co-morbidity between mood disorders and drug dependence.

Contents

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1. Introduction

Epidemiological data indicates that the incidence of drug abuse among depressed patients is substantially higher than expected from the individual rate of these disorders (Davis et al., 2008). However, it is unclear whether drug abuse increases the risk of depression or vice versa (Fergusson et al., 2009).

From a theoretical perspective, it is intriguing that alterations in reward and motivational processes could be central to the development and symptomatology of both depression and drug dependence. As such, the hypothesis of self-medication of depression with drugs of abuse could be discussed as an explanatory concept for understanding the observed clinical comorbidity of depression and drug dependence. High positive correlations (0.38–0.56) were reported between mood disorders and drug dependence (Kessler et al., 2005). For instance, the prevalence of lifetime alcohol dependence could be as high as 20.3% in people with combined lifetime anxiety and depressive disorders (Boschloo et al., 2011). Drug-induced adaptive changes within the neurocircuitry could underlie the core features of both disorders. Paradoxically, the neuroadaptations following repeated drug administration and/or during drug-withdrawal usually oppose those induced by the acute effects of the drugs. Therefore when drug administration is discontinued, many of these adaptations (detailed in Section 3 of this review) may remain unopposed, which may constitute the basis of the withdrawal syndromes. The opponent-process theory of emotion (Solomon and Corbit, 1974) predicts a reversal of emotional valence during motivational or affective withdrawal in a homeostatic control mechanism.

Abnormalities in dopaminergic transmission in the nucleus accumbens (NAc) and ventral tegmental area (VTA) are well-described by numerous studies investigating the neurochemical consequences of exposure to drugs of abuse (Radke et al., 2011). The amygdala is another brain region of interest relevant to drug abuse and mood disorders, especially anxiety. Interestingly, distinct profiles of anxiety and dysphoria have been suggested during morphine withdrawal and each reflect changes in distinct neural systems (Rothwell et al., 2009). D'Souza and Markou (2010) recently reviewed the neural substrates involved in drug withdrawal focusing on the anhedonia experienced after cessation of psychostimulant administration. Other recent reports have discussed the anxiety-like states during drug withdrawal taking into consideration the interaction between catecholamines (DA and NA), CRF and glutamate in VTA and the extended amygdala (Koob, 2009a,b; Corominas et al., 2010; Erb, 2010; Koob and Volkow, 2010). As syndromes, anxiety and mood disorders share several features. Both can be treated with Selective Serotonin Reuptake Inhibitors (SSRIs) as an initial pharmacological intervention (Katzman, 2009; Baldwin et al., 2010). However, since some key pathological differences exist between anxiety and depressive disorders (Craske et al., 2009; Martin et al., 2010), it is important that these are addressed separately (see Chourbaji et al., 2011 for an illustration using mouse models).

Despite evidence for the beneficial effects of antidepressant drugs that act by modulating serotonin levels in the brain such as the SSRIs on affective and addiction-related behaviours, as well as the availability of substantial data of depressed patients having reduced hippocampal volumes, there is yet to be a review focusing on serotonin (5-HT), hypothalamic-pituitary-adrenal (HPA) axis and hippocampal plasticity in the context of withdrawal-induced depression. Indeed, the neurobiological mechanisms underlying the withdrawal from psychoactive drug may involve alterations within the serotonergic and stress systems that have been hypothesized to contribute to the negative affective states associated with abstinence from the drug in question (Watkins et al., 2000) and are well-established as being the key systems involved in the pathophysiology of depression. Therefore, this review aims to introduce the behavioural as well as the neurochemical and plasticity changes in depressed patients and several animal models of depression. Following, we provide a more in-depth discussion of the specific roles of serotonergic neurotransmission, the HPA axis and hippocampal plasticity in depression-associated with withdrawal from chronic drug intake.

2. Drugs of abuse: from historical traces to animal models

The history of the human race is steeped with evidence of drug use—for medicinal or recreational intentions. Evidence gathered from the mummified bodies of the Tinawaku, predecessors of the ancient Incan race flourishing in Peru and Bolivia from 1000 to 200 B.C., suggest the use hallucinogens (Ogalde et al., 2009). Marijuana has existed in written records for 2000 years and its use as an anaesthetic can be traced back to China some 5000 years ago. Sumerian clay tablets from 500 years ago reflect the use of narcotics. The oldest bottle of wine from the Roman civilisation dates back to 325 A.D. while recent archaeological evidence indicates that wine was being produced as far back as 6500 years ago. It is human nature to seek pleasure, and the wonton display of excess embodied by Greek and Roman feastings have now been replaced by its modern version—drugs of abuse, resulting in the social evil we know as drug addiction.

The recognition of drug addiction as a health and social problem is fairly recent given its illustrious history. It was only in 1906 that the first national drug law in the United States of America (Pure Food and Drug Act of 1906) was passed mandating the accurate labelling of patent medicines containing opium and certain other