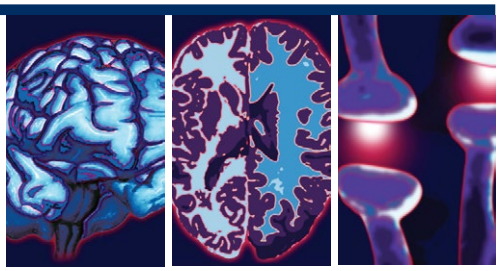
Review



Addictions and Stress: Implications for Propofol Abuse

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Abstract

Advances in neuropsychosis have concluded that addiction is a chronically relapsing brain disorder. Cue-, drug-and (or) stress- primed reinstatement play important parts on the development of drug abuse. Stress is a key factor in the acquisition and persistence to illicit drugs and psychostimulants such as cocaine, heroin, ketamine, alcohol and nicotine. When the access to the drug is prevented, the emergence of a negative emotional state will trigger the crucial neurochemical elements involved in the brain reward and stress systems. In this review, we will first discuss the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in the compulsive drug taking. The prominent components of stress-responsive system including CRH, vasopressin and glucocorticoid will be considered as the dark side drivers in addiction. And then we will reveal the essential mechanisms of propofol abuse as well as its association with HPA axis responsiveness. Propofol is a widely used intravenous anesthetic. However, in recently year's propofol has been demonstrated as an addictive drug in anesthesiology. Converging evidence suggests the activation of mesocorticolimbic system and the interactions between the reward and stress system can partly illustrate the specific mechanisms of propofol abuse. Future directions in research are identified to increase understandings of the mechanisms by which stress may increase risks of drug addiction.

Keywords

Addiction, HPA, Propofol, Dopamine, ERK, Glucocorticoid

Introduction

Addiction has been conceptualized as a chronically relapsing brain disorder characterized by (i) a compulsion to seek and take drugs,(ii) loss rational control over drug intake, and (iii) when access to the drug is prevented comes emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) that defines a motivational withdrawal syndrome [1]. Propofol is an intravenous anesthetic that has obvious reward and relapse effect [2,3]. It affects a large group of human, severely jeopardizes life quality and burdens hygiene system. There are increased reports of propofol creational use worldwide in last 10 years [4]. Current epidemic studies also show that propofol misuse is an important marker of death risk [5,6]. It's an urgent task to extend our understanding of the molecular and neural mechanisms underlying this brain disorder.

Stress is a word used to describe an organism's response to a stressor that are challenging emotionally and physiologically. Multiple systems anticipate in this "fight-or-flight" response, among which is the activation of hypothalamus-pituitary-adrenal (HPA) axis. The axis involves the release of corticotrophin-releasing-hormone (CRH) and vasopressin from the hypothalamus which stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH). And then ACTH can stimulate the adrenal glands to secrete cortisol. The HPA axis is subject to negative feedback regulation as well. Clinical research suggests stress and

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drugs exhibit cross-sensitization, whereby drug experience facilitates stress response and vice versa [7,8]. Compared to healthy control, the plasma level of ACTH and cortisol is raised in drug addictive group [9]. When presented with cortisol, addicted individuals exhibit a strong cocaine caving [10].

To promote the treatment of stress reduction in addicts, we should first identify the neurobiological mechanisms underlying the interactions between and stress and drugs. The review will focus on how the stress hormones potentiate drug-taking as well as how drugs change stress response. Furthermore, we will also reveal the stress related neurobiological alterations in propofol addictive rats and the implications of these alterations in developing specific treatment.

Hypothalamus-Pituitary-Adrenal (HPA) axis in Stress and Addiction

■ Corticotrophin-Releasing-Hormone (CRH)

Released by hypothalamic paraventricular nucleus (PVN), CRF exerts its systemic effects which can control behavior, hormonal and sympathetic responses to stress. It not only serves as the primary mediator in the HPA response but also as an independent role in drug addiction [11]. In the brain, CRH binds to two types of G- protein coupled receptors, CRF receptor type 1 (CRFR1) and CRF receptor type 2 (CRFR2). Vale et al first demonstrated that CRF initiates the HPA axis by its binding into CRFR1 in the anterior pituitary [12]. In addition, however, CRFR1 are widely distributed in other brain sites. These sites include the paraventricular nucleus of the hypothalamus, the basal forebrain and the brainstem [13].

The dissociable, non-endocrine roles of extra hypothalamic CRF systems are hypothesized to account for drug withdraw specifically. The persistent activation of CRF release and immunoreactivity results from drug withdraw [14,15]. In alcohol dependent rats, withdrawal models stimulate CRF system in the central nucleus of the amygdala (CeA) [16]. CRF levels in the CeA also increased during precipitated withdrawal from chronic nicotine [17]. *Crh* mRNA transcription in CeA and nucleus accumben (NAc) is also enhanced in nicotine withdrawal rats [15,18]. Furthermore, CRF antagonists alleviate negative emotional symptoms of acute and protracted withdraw [17,19,20]. CRF primarily engaged in maintaining drug abusers' emotional homeostasis via downregulation of brain reward systems and upregulation of brain stress systems [20-22]. With increased CRF levels, cession of drug taking provokes self-administers' aversive state, which leads to drug seeking behavior.

The dysfunction of CRF system influences many downstream targets. CRF could contribute to modulate ventral tegmental area (VTA) dopamine neurons via potentiating glutamate release and excitatory transmission [23,24]. Furthermore, CRF can also facilitate dopamine signaling in the NAc [25]. It's likely that CRF can sensitize mesolimbic dopamine system that plays a key role in the rewarding response to drug. However, there are conflicting reports that CRF is also able to decrease dopamine release in the NAc. Intracerebroventricular injection of CRF can blunt electricity stimulated reward effect [26]. It's possible that the aversive state of drug withdraws and decreased reward effect associate with CRF contribution are dopamine independent. Another downstream target of CRF in addiction is dynorphin and the kappa opioid system [27]. Valdez, *et al.* shows that selective CRF1 receptor blocks the kappa opioid receptor agonist-induced reinstatement to cocaine seeking in squirrel monkeys [28].

■ Vasopressin

Vasopressin (AVP), also known as antidiuretic hormone (ADH), is a neurohypophysial hormone that is synthesized in the hypothalamus and stored in vesicles at the posterior pituitary. Early work demonstrated AVP contributed to the motivational properties of heroin and cocaine [29-31]. There are three subtypes of AVP receptors: V1a, V1b, and V2. While V2 is located in the kidney and produces the antidiuretic effect, V1a and V1b, which are both expressed in extended amygdale and anterior pituitary, are supposed to be involved in the modulation of HPA activity and drug addiction [32,33].

A growing number of evidence suggests that AVP/V1 systems in the hypothalamus, amygdala and other brain regions represent important elements in the neurobiology of drug abuse. During protracted withdrawal, the level of hypothalamus AVP gene expression seemed to elevate in parallel with HPA activity [32]. Cocaine withdrawal increases AVP mRNA levels in rat medial amygdala [34]. Amygdalar AVP mRNA

increase is further found during early heroin withdrawal and also after foot shock in the rat withdrawn from heroin for 2 weeks [33]. Borrero, *et al* revealed AVP played a functional role within the NAc on the acquisition and expression of cocaine conditioning response [35]. An interesting study suggests cocaine exposure leads to the indifferent paternal care via disrupting central AVP signal [36]. Furthermore, Selective V1b antagonists dose-dependently attenuated stress-induced and heroin-induced reinstatement, and blunted the HPA activation by stress [33]. It's promising that the stress-responsive AVP/V1b system will be the new therapeutic target for drug relapse.

■ Glucocorticoid

As a consequence of stressful stimuli, the active HPA axis releases glucocorticoid hormones (GC), corticosterone in rodents and cortisol in humans. Short-term GC exerts beneficial effects on adaptive performance and cognition response, while prolonged and/or repeated increased levels of GC induced by chronic stress can trigger a lot of maladaptive conditions, some of which may lead to drug addiction. For example, corticosterone replacement is sufficient to restore or maintain cocaine-induced locomotor sensitization, self-administration behavior and relapse susceptibility following adrenalectomy [37-39]. In human addicts, stress-, cue-, and drug-induced craving for cocaine are associated with elevated cortisol [40,41].

GC activates the mammalian brain via mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), which result in celluar signaling cascades that ultimately target various gene transcriptions. GR is a ubiquitous transcription factor mediating adaptation to stress and addiction. GR is widely expressed in the reward related brain circuitry, including NAc, prefrontal cortex(PFC), VTA ,bed nucleus of stria terminalis(BNST) and so on [42-45]. Several investigations have been taken to reveal the interaction between GR and drug abuse. Systemic GR antagonism can dose-dependently attenuate the breaking point for cocaine reinforcement under progressive ratio schedules [46]. Employing the technique of selective *GR* gene inactivation, Baril, *et al* demonstrated GR in dopaminoceptive neurons is dispensable for behavior responses to morphine [47]. Alcohol-induced behaviours in female mice can be inhibited in the presence of a GR antagoinists [48].

GR mediated genomic effects via transcriptional regulation and rapid non-genomic effects in drug abusive organisms. In post-natal day (PND) 45 cocaine addictive rats, there are an enhanced activities of GR transcription as well as spine actin network in the PFC. These results suggest that the hyperactivation of cortical GR may affect spine dynamism through the mechanisms of navigating some specific genomic transcription [49]. Some GR related neurotrophic signaling have also been demonstrate, after chronic morphine and cocaine injection, the activity of glucocorticoid-inducible kinase1(SGK1) was increased robustly in VTA [50]. In term of genomic-independent mechanisms, McReynolds et al first reveal the cooperation of corticosterone with the organic cation transporter3(OCT3) mediates corticosterone effects on drug-seeking behavior [51]. Consistent with previous *ex vivo* discover that glucocorticoids rapidly decrease the uptake of dopamine by crude striatal synaptosomes [52], the results of Graf's research demonstrates corticosterone treatment is able to decreases dopamine clearance in the NAc via inhibiting uptake2-mediated transport [53].

The Neurobiology of Propofol Addiction

■ The role of mesolimbic dopamine system

Dopamine (DA) is the primary catecholamine neurotransmitter in the brain. DA neurons originate in the substantia nigra (SN) and VTA and project to the striatum, cortex, limbic system and hypothalamus. Through these connection fibers, DA achieves many physiological functions, such as the control of coordinated movements as well as reward-related behaviors [54-56]. It's well accepted the mesocorticolimbic dopamine system ,which is consist of cell bodies in VTA that project to NAc, underlies drug reward effect and contributes to relapse behavior. Pain et al. employed the in vivo brain microdialysis method to assess the DA concentration in NAc, they found that DA was decreased at the smallest dose of 9 mg/kg, whereas it was robustly raised at the subanesthetic (60 mg/kg) and anesthetic (100 mg/kg) doses, indicating propofol's abuse potential [57]. In vitro, 1.5 × 10(-4) mol/L propofol could inhibit dopamine uptake reversibly with a non-competitive profile [58]. Consistent with these findings, our previous work successfully established the propofol addiction model and showed that rats could develop strong self-administration behavior within a 15- day training

session [2]. Furthermore, we also extended our understandings of the specific mechanism that regulates DA release from the midbrain DA neurons. Microinjection of $GABA_B$ receptor agonist baclofen (50 and 100 ng/side) into the VTA could significantly decrease the number of active responses and total infusions of propofol, however, $GABA_A$ receptor antagonist bicuculline (0.25 mg/kg, ip) produced the contrary outcome. The result suggests propofol can activate $GABA_A$ receptor and increase the activity of DA neurons in VTA through disinhibition, and stimulation of $GABA_B$ receptors in VTA may counteract the reinforcing properties of propofol [59].

Dopamine receptors belong to the family of seven transmembrane domain G-protein coupled receptors. By far, five different subtypes of DA receptors have been indentified. Based on their structural and pharmacological properties, DA receptors can be divided into two groups: the D1-like receptors, which stimulate intracellular cAMP level, comprising D1 and D5 [60,61], and the D2-like receptors, which inhibit intracellular cAMP levels, comprising D2,D3 and D4 receptors [62-64].

We demonstrated systemic administration of D1 receptor antagonist SCH23390 (10, 30, 100ug/kg, i.p.) dose-dependently decreased the behavior rate of propofol taking, in addition, we also indentified the activation of NAc D1 receptor as a critical mechanism in the reinforcement of propofol [2].

■ The role of extracellular signal-regulated kinase

Addictive drugs modulate the expression of neuroplasticity-related genes and ultimately disturb intracellular signaling cascades associated with addiction [65]. Within the reward system, including dopaminoceptive neurons of the striatum and NAc, both cocaine and morphine activate common signaling cascades including the extracellular signal-regulated kinase (ERK) pathway [66]. Activated by D1 and D2 receptors, ERK takes parts in different physiological responses, such as cell death and development, as well as synaptic plasticity [67,68].

Our recently work tests the hypothesis that the activation of ERK pathway in the NAc drives the maintenance of propofol self-administration in rats. In experiment 1, we used pharmacological intervention to investigate how drug seeking behavior and ERK expression change after systemic inhibition of D1 receptor. The data shows pretreatment with SCH23390 can not only dose-dependently decreased the expression of p-ERK in the NAc but also impaired the behavioral responses to propofol. Furthermore, the authors demonstrate that intra-NAc injection of MEK inhibitor, U0126 attenuates the propofol self-administration. Taking together, we suggest ERK signal transduction pathways coupled with D1 receptors in NAc may involve in the propofol reward effects [3].

■ The role of glucocorticoid receptor

Stress and GCs potentiate dopaminergic transmission and influence reward seeking and intake in laboratory animals [69,70]. It remains currently unclear, however, whether GR acting in particular dopamioceptive neurons can influence the motivation of rats to self-administer propofol. Answering this question is an essential step toward understanding the molecular mechanism that mediates the interaction between stress and propofol abuse.

In our research, first we observed the seemingly paradoxical behavior change after injection intraperitoneally with GR angoist (dexamethasone) and GR antagonist (RU486) respectively. Selective deletion of GRs in NAc attenuated cocaine self-administration as well as cocaine-induced behavioral sensitization [47,71]. Consistent with this, we demonstrated that RU486, an antagonist of GR, inhibited propofol self-administration in rats. Interesting results came with the similar damping effect of the GR agonist dexamethasone. It's possible the decreased level of serum corticosterone, caused by the negative feedback regulatory mechanisms, contributed to the counteract the propofol reward effects. To further elucidate the specific molecular mechanism, the expression of dopamine D1 receptor in the NAc and the plasma concentration of cortisocterone was examined, we have found the indirect influence of dexamethasone on D1 receptor level in NAc. These findings provide evidence that GR was responsible for glucocorticoid-mediated increase in propofol reinforcement [72].

Conclusion

The effort made in this review to link stress hormones with changes in neuron physiology in mesocorticolimbic circuitry is clearly demonstrated by a dearth of experiments identifying cause and effect mechanisms. Indeed,

currently available medications in development targeting CRF, vasopressin, and glucocorticoid receptors may represent powerful tools to minimize the effect of stress on addiction.

But here come the question: What is it they all have in common? Is there a unifying pathway that in so many cases leads to the function of stress as a "stage setter" for drug use? For better understanding this, more advanced technological approaches should be employed to explore the underlying neurobiology of drug addiction. For example, optogenetics technologies, which enable fast and precise control over targeted circuit elements with intact tissue and behaving mammals [73], it can isolate single brain regions by genetic manipulations, and replace the intra-cranial injection of receptor-binding drug solutions with the highly controllable optical stimulation. Collectively, the contribution of stress to drug use likely varies across different drugs and individual addicts, we are optimistic that advances in the understanding of the interaction between the stress and addiction, will lead to the effective stress-targeting treatment.

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