



## Review Article

# Overview of withdrawal syndrome mechanisms in different substance abuse addictions: Neuronal circuits and transmitters

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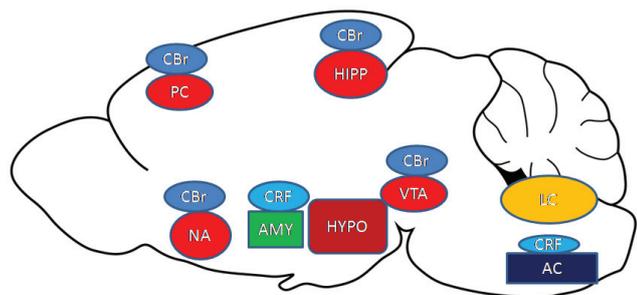
## Abstract

Substance abuse is one of the major concerns of human societies. Many problems exist for controlling drug abuse that profoundly influences treatment. One of the most important and prevalent problems is Withdrawal Syndrome (WS). The WS describes a host of unpleasant symptoms that develop in the withdrawal period. WS should be suppressed in the withdrawal period because in the presence of WS dependence on drugs will continue. Using the drug to which one is addicted is the most effective way to suppress the withdrawal syndrome, which is why many users relapse after a period of abstinence. The purpose of this review article is to describe the basic brain mechanisms that are responsible for the emergence of WS that cannot be tolerated in the abstinence period. This may be helpful for a better understanding of the nature of WS in the withdrawal period for implementing the best approach with new insights for highlighting new horizons for future goal-directed studies. The important topics in this regard are non-related brain areas based on recent studies that have been proposed. They have included the rewarding center, endogenous cannabinoid system, corticotropin-releasing factor, locus coeruleus, and orexin system. According to the above facts, this syndrome arises with different mechanisms, and a multi-approach treatment toward this syndrome is required.

## Introduction

Withdrawal Syndrome (WS) is undesired and unpleasant symptoms and signs that occur after cessation of abusing addictive substances [1,2]. Withdrawing from addictive substances may occur as a consequence of personal decision or in a clinical setting under the supervision of a clinician. There is a difference among individuals in the emergence of withdrawal signs and symptoms [3,4]. Needless to say, without WS, getting rid of substance abuse is much easier [5]. In the absence of WS, the development of dangerous addiction that manifests as compulsive drug seeking and taking behavior will be hindered [6]. From this prospect, treatment toward these signs and symptoms will reduce relapse to drug abuse [7]. WS is the emergence of unpleasant symptoms that has been well described in animal models and humans. The emergence of WS in the abstinence period will increase relapse to abuse

drugs. So it would be reasonable to think that for controlling dependence, the undesired symptoms and signs should be suppressed. WS has been described as two-component: affective and somatic [8]. Both cause relapse to addiction. Affective symptoms include dysphoria, irritability, and anxiety, which might contribute to aversively motivated drug seeking [9] and somatic especially in animal models include diarrhea, facial fasciculations/teeth chattering, paw tremors, head shaking, swallowing, salivation, chromodacryorrhea, ptosis, abnormal posture, erection/ejaculation/genital grooming, and irritability [10,11]. This article aims to delineate the origin of such signs and symptoms and introduce new potential insights for therapy in such cases. However, based on recent studies, more than one region in the brain produces WS, independent of each other. So, they have been discussed separately. Also, it is noteworthy to say more studies especially in humans should be down to fully understand the context in which these symptoms appear. In Figure 1, a brief overview has been illustrated.



**Figure 1:** The above figure shows a different part of brain structures that are involved in withdrawal syndrome (WS) production.

Reward circuit components including Nucleus Accumbens (NA), Prefrontal Cortex (PC), Hippocampus (HIPP), and ventral tegmental area (VTA) are actively involved in WS. This circuit independently and also by the action of other systems produces WS. The Endogenous Cannabinoid System (ECS) is widely distributed in the brain and its receptors CB1 and CB2 are also found in different areas. CB receptors (CBr) are found on the reward circuit component. Other mechanisms for ECS are not well understood. Corticotropin-Releasing hormone (CRF) is mainly secreted by the Hypothalamus (HYPO) and this hormone in producing WS has two mechanisms: direct action by stimulating the amygdala (AMY) and by an indirect pathway through activation of the autonomic center (AC). Hypothalamus (HYPO) also secreted orexin that was newly known for its direct action in the production of WS. Locus coeruleus (LC) secretes norepinephrine that causes the emergence of WS.

### Reward circuit

Dopaminergic neurons in a reward circuit are a collection of neuronal structure that is responsible for incentive salience that is characterized by a craving for reward, motivation, learning, and mood [12,13]. The neuronal circuit connects different parts of brain structures such as cortical and midbrain components [14,15]. This important neuronal circuit is composed of different types of neuronal projections that are closely interconnected such as glutamatergic interneurons, GABAergic Medium Spiny Neurons (MSNs), dopaminergic projection neurons, and orexinergic projection neurons [16].

The reward system includes many different parts but little is known about the importance of these regions in producing WS. They have included the ventral tegmental area, striatum, substantia nigra, prefrontal cortex, cingulate cortex, insular cortex, hippocampus, hypothalamus, thalamus, subthalamic nucleus, globus pallidus, ventral pallidum, parabrachial nucleus, amygdala [17]. There are pieces of evidence that support reward center efficacy is necessary for the withdrawal period. It has been before well established that the crucial element in establishing addiction is overexpressed  $\Delta$ FOS after dopamine release. Other behaviors that are established after dopamine release is self-administration and reward sensitization and cross-sensitization [18]. However, this may be the psychologic element of WS that may be related to drug abuse memory and not a physical component [19]. However, other studies explain other mechanisms for physical WS. WS can be

explained in the best way with the concept of allostasis, the phenomena in which organisms tend to maintain the homeostasis despite stress [20,21]. Strong evidence supports the fact that the reward center's proper function is disturbed as the consequence of drug abuse [22–25]. Therefore, brain reward deficit may be a common affective component of withdrawal signs. Reward center insufficiency manifests itself in the withdrawal period through affective and emotional signs that include anxiety-like behavior, restlessness, and depression [26]. It is well established that for successful treatment of addiction some patients need psychotherapy. This is due to the presence of this affective component of withdrawal syndrome [27]. Recently the habenulo-interpeduncular region that is located in the thalamus is important to produce WS [28]. Habenulo-interpeduncular region has a widespread connection to the reward center and helps the better function of the reward center and it has been suggested for better treatment of addiction this region should be taken into consideration [29].

### Endogenous cannabinoid system

Endocannabinoid System (ECS) is a biological system composed of Endocannabinoid, which are endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors. This system has two types of receptors: CB1 and CB2 [30]. This system in normal physiologic condition causes no disturbance in normal body function, but upon an increase or decrease in ECStone, pathologic condition develops [31]. That is the result of altered expression of CB receptors, endocannabinoid metabolizing enzymes, and synthetic pathways. The CB1 receptor is a G-protein coupled receptor that mediates the psychoactive properties of delta-9-tetrahydrocannabinol (THC) [32]. CB2 is most abundantly found in the animal brain such as rats in areas other than the reward circuit. CB1 is mostly concentrated in pre-synaptic areas and contrast CB2 mainly is located in post-synaptic areas [33]. However, the modulatory role of ECS on the reward center is thought to be related to the presence of cannabinoid receptors on VTA [34,35]. This action is not a direct action but rather is an indirect effect on retrograde synaptic transmission [36]. Previous studies have shown that the establishment of addiction can occur through ECS. However, if the establishment of addiction occurs as the result of the development of WS is not the case because WS occurs usually after the establishing of addiction. Many studies support the theory that ECS has a role in the establishing of addiction. Previous studies suggest that ECS has a role in the emergence of withdrawal syndrome [37]. This possibility rises when WS occurred after the chronic administration of cannabinoid antagonists. These observations raised the possibility that the cannabinoid antagonist produced rewarding effects, presumably by blocking either a dysphoric action or an inhibition of reward circuits produced by endogenous cannabinoids [38,39]. Experiments with other addictive drugs had the same result and confirm that ECS can be used as an effective target for the treatment of WS [40–43]. ECS also mediates the rewarding effects of an addictive substance such as nicotine [44]. This suggests the pivotal role of ECS in the emergence of WS in the abstinence period. These findings suggest a new therapeutic strategy for the treatment of addiction [45].

## Corticotropin releasing factor (CRF)

Corticotropin-Releasing Factor (CRF), a 41 amino acid-containing peptide, is secreted by the hypothalamus [46]. Besides the hypothalamus, this hormone has been discovered in cerebral cortical interneurons, the limbic system, brainstem, and spinal cord [47]. CRF receptors are G protein-coupled receptors and are two types: type 1 and type 2. Besides the pituitary, CRF receptors are also present in other brain areas such as the amygdala, locus coeruleus, and hippocampus. CRF is thought to be responsible for a wide range of neuropsychiatry disorders such as anxiety, depression, and also in substance abuse withdrawal period. It is the main hormone that is secreted in response to stress not only endocrine but also the autonomic and behavioral responses to stress [46]. Based on their important role in stress regulation different studies have been done to evaluate the efficacy of therapy [48]. Based on these studies CRF agonist and antagonist can be used in clinical settings but more studies are needed [49,50]. CRF has divergent effects on addiction. However, the role of CRF in the withdrawal period has been well established. Relapse can occur as the result of brain centers or through indirect pathways that are responsible for keeping the body in a steady state. The indirect pathways mainly occur through the insufficiency of the brain to control the body that is called allostasis. In this case, the body cannot adapt to new conditions and withdrawal signs occur by the activation of the autonomic system [51]. In this type of relapse is the appearance of anxiety, the emotional component of withdrawal syndrome occurs as the result of autonomic overstimulation [52,53]. In direct pathways, it has been proposed that CRF by direct stimulation of CRF receptors will cause the emergence of anxiety in the withdrawal period and this may increase the risk of relapse [54]. In different studies, CRF receptor antagonist diminished withdrawal syndrome [55, 56]. Also, another experiment revealed that CRF2 antagonist reduces the somatic expression of WS [57]. However, it should be noted CRF has two types of receptors including CRF1 and CRF2 and both types of blockage would diminish withdrawal signs [58,59]. The antagonist of CRF receptors also prevents a deficit in brain reward proper function [60]. Some studies have used systemic administration of agonist and antagonist of CRF receptors and localization of such useful effects has not well been described.

## Locus coeruleus (LC)

Locus coeruleus is a nucleus in the pons of the brain stem that is the origin of physiological brain response to stress [61]. Norepinephrine is the brain mostly synthesized in this nucleus [62]. The locus coeruleus is responsible for mediating many of the sympathetic effects during stress [63]. In a stress state norepinephrine beside activation of the hypothalamic-pituitary-adrenal axis directly increase sympathetic flow [64]. Moreover, LC in a stress state increases cognitive and emotion through the prefrontal cortex and nucleus accumbens, respectively [65]. Locus coeruleus has been hypothesized as one of the brain regions that most responsible for the occurrence of Withdrawal Syndrome (WS) [66,67]. The LC is rich with a cluster of noradrenergic neurons [68] and this nucleus has a

high density of opiate receptors especially  $\mu$  and  $\kappa$  receptors [69–71]. The destruction of LC neurons reduces physical signs of opiate withdrawal [72]. Also, acute opiate administration in animal models reduces the firing rate of LC neurons [73]. However, after chronic administration reverse occurs and LC neurons will be hyperactive and will result in WS [74]. More studies revealed that LC is the main site of withdrawal syndrome and another afferent may potentiate this region as the origin of this syndrome. These afferents include the nucleus Paragigantocellularis (PGi) in the rostral ventrolateral medulla and the medial perifornical area of the nucleus propositus hypoglossal (PrH) in the dorsomedial rostral medulla [75,76]. Not only opiate receptors but also NMDA receptors and AMPA receptors [77–82] have been known for this syndrome. In another study excitatory amino acid input has been proposed as the main mechanism for the occurrence of WS [83]. Enhanced serotonergic neurotransmission diminishes an augmented excitatory amino acid input to LC neurons that is responsible for most of their hyperactivity during opiate withdrawal [84]. More studies showed an injection of muscimol, a GABA<sub>A</sub> receptor agonist [85–87], and baclofen, a GABA<sub>B</sub> receptor agonist [88,89], reduced naloxone-induced WS in morphine-dependent mice. Also, dopamine receptors especially D1 in LC interfere with the occurrence of WS [90]. Recent studies revealed more mechanisms for this purpose. Recently it has been proposed that orexin plays an important role in drug addiction [88,91]. Orexin neurons are located in the lateral hypothalamus, perifornical area, and dorsomedial hypothalamus and have extensive projections throughout the brain especially LC [92, 93]. The blockage of orexin receptors in LC attenuates signs of naloxone-precipitated morphine withdrawal [94]. Galanin also inhibits the firing of LC neurons [95]. Modulation of galanin receptors in LC reduces WS signs [96].

## Orexin system

Orexin, also known as hypocretin is a neuropeptide that is secreted by a cluster of neurons in the lateral hypothalamus and perifornical [97]. Orexinergic neurons receive different kinds of signals and projects richly to different parts of the brain such as the reward circuit. However, considering the number of neurons there are only 10,000 to 20,000 neurons in related brain areas. There are two types of orexin peptides (A and B) and two G-protein coupled receptors (orexin 1 and orexin 2) [98,99]. Connectivity and functionality of the orexin neurons in the two related brain areas known as lateral hypothalamus and perifornical are different. Orexinergic neurons in the lateral hypothalamus are closely associated with reward-associated functions such as Conditioned Place Preference (CPP) and richly innervate the related brain areas such as the Ventral Tegmental Area (VTA) and prefrontal cortex [100] but neurons in perifornical areas are involved in autonomic function [101]. This system is inhibited and stimulated by different neurotransmitters. GABA (Gamma-Amino Butyric Acid), serotonin, and noradrenalin suppress the system and by contrast dopamine, cholecystokinin, neurotensin, oxytocin, and vasopressin activate this system. Glutamate can tonically affect orexinergic neurons [102]. This relatively newly



discovered system (1998, for the first time) has been known as an important role in addiction. Recent shreds of evidence that showed this system can affect the addiction process come from studies that showed administration of orexin blockers hinder methamphetamine, nicotine, cocaine, alcohol, and opioids addiction [103–107]. Other studies showed orexin not just effective for the establishment of addiction but also can influence the reinstatement of pre-existing addiction [108]. The study result about nicotine is not consistent. For example, orexin-1 has reduced nicotine self-administration but other types cannot establish the same result [108]. It is known that naturally reinforces such as sugar and also addictive drugs both positively affect the reward circuit and this sense of orexin has a similar effect and is affected by both natural and addictive substances [109]. Based on the above study results, different sets of clinical trials were conducted to evaluate the orexin-targeted therapy for dependence. Suvorexant is a synthetic orexin-like agent that has been recently been used as a novel treatment for cocaine-dependence and the preliminary result showed successful results [110]. In nicotine dependence, the studies are in the first steps and more studies should be done to get precise knowledge about the nature of orexin in nicotine dependence [111].

## Conclusion

In this review article different mechanisms that cause the emergence of withdrawal syndrome were discussed. WS will not restrict one area in the brain but are related to different areas. Withdrawal syndrome is a great problem for stopping addiction because they are undesired and unwanted signs and symptoms and they are unrelated issues in the withdrawal period. In the absence of them, individuals will progress to quitting addition without difficulty. So, a better understanding of the nature of mechanisms behind them may help to establish effective management of this syndrome.

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