Review Article

Potential Involvement of Apelin/APJ System in Addiction and Neuroprotection Against Drugs of Abuse

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Abstract

Addiction, characterized by compulsive drug-seeking behavior and impaired self-control, remains a significant public health concern. Understanding the neurobiology of addiction is crucial for identifying novel therapeutic targets and further developing effective treatments. Recently, the apelin/APJ system, an emerging signaling pathway, has attracted attention for its involvement in various neuropsychiatric disorders. The cross-talk between the apelin/APJ system and hypothalamic mu opioid signaling, as well as its heterodimerization with kappa opioid receptors (KORs), supports the potential relevance of this system to addiction. Moreover, several protective effects of apelin against various addictive substances, including methamphetamine, morphine, and alcohol, underscore the need for further investigation into its role in substance use disorder. Understanding the contribution of the apelin/APJ system in addiction may offer valuable insights into the underlying neurobiology and pave the way for novel therapeutic interventions in substance use disorders. This review provides a concise overview of the apelin/APJ system, emphasizing its physiological roles and highlighting its relevance to addiction research.

Keywords: Apelin, APJ, Addiction, Substance use disorder, Drug abuse

Introduction

Addiction can be delineated as a persistent and recurrent disorder, displaying an inherent compulsion to actively pursue and consume a particular substance, coupled with a diminished ability to exert control over intake. Notably, the emergence of a detrimental emotional state becomes apparent upon the obstruction of access to said substance.[1] The understanding of the neurobiology underlying addiction has advanced through the investigations of animal models and, more recently, by means of brain imaging investigations conducted on individuals affected by addiction. The activation of brain reward systems occurs upon the administration of drugs of abuse, and extensive research conducted on drug addiction has predominantly elucidated the neurocircuitry associated with the reward process.[2]

Drug addiction disrupts multiple brain regions and circuits, each of which is likely to contribute differentially to the intricate phenotype observed in addicted individuals. Although much focus has been put into the role of opioid system,[3] dopaminergic signaling,[4] and glutamatergic neurotransmission,[5] in drug reward and development of addiction, emerging signaling systems with multiple implications in the central nervous system (CNS) have gathered attention. In this review, we aimed to gather evidence on the potential involvement of a relatively new system called apelin/APJ in addiction. We first provide an overview of the system along with its various neuroprotective roles. Based on the protective effects of apelin against drugs of abuse and its interplay with opioid receptors (OPRs), we further raise hypotheses on how apelin/APJ signaling might be a potential system worth exploring in the context of addiction.

An overview of the apelin/APJ system

APJ, discovered by O'Dowd in 1993, is a G protein-coupled receptor (GPCR) derived from the human gene.[6] Initially characterized as an orphan GPCR, APJ is composed of 380 amino acids and exhibits a hydrophobic region with a homology of 40% to 50% to the angiotensin type I receptor.[7] Later in 1998, Tatemoto et al successfully isolated and purified the endogenous ligand of APJ from bovine gastric secretions. They subsequently named this ligand "apelin".[8]

Apelin is expressed from the APLN gene and is initially synthesized as a 77-amino acid pre-propeptide.[9]

Proteolytic cleavage of the pre-proapelin molecule by specific proteases leads to the generation of various biologically active apelin peptide forms, such as apelin-13, apelin-12, apelin-17, and apelin-36s. Apelin-13 and apelin-36 are considered to be the most prevalent and biologically active fragments among the different apelin peptide forms.[10,11]

Both apelin and APJ mRNA exhibit broad expression patterns in various organs and tissues, encompassing the CNS, cardiovascular system, gastrointestinal tract, lung, kidney, and placenta.[12,13] Apelin is mostly known for its pivotal physiological roles in cardiovascular physiology by regulating heart contractility, mediating vasorelaxation and facilitating neoangiogenesis.[14,15] Furthermore, apelin is involved in bone physiology, modulation of immune system function, maintenance of body fluid homeostasis, and energy metabolism.[16,17] The extensive involvement of apelin/APJ system in different physiological functions of the body has made it a potential target in developing drugs, particularly gathering attention as an emerging therapeutic target for neurological diseases.[18]

Role of apelin/APJ system in various neuropsychiatric disorders

The intricate interplay between molecular signaling pathways and the complex manifestations of neuropsychiatric disorders has captivated the attention of researchers worldwide. Among the fascinating avenues of investigation in recent years is the apelin/APJ system, that has emerged as a potential key player in the pathophysiology of numerous neuropsychiatric disorders.[19] This system has increasingly garnered attention for its involvement in diverse aspects of brain function and behavior. In this section, we explore the connections between the apelin/APJ system and several neuropsychiatric disorders, shedding light on its potential as a novel therapeutic target and offering fresh insights into the neurobiology underlying these debilitating conditions.

Initial investigations have demonstrated that apelin-13 exhibits a dose-dependent capability to mitigate brain injuries and post-ischemic cerebral edema. These effects are believed to be achieved through the inhibition of apoptosis.[20] Subsequent studies have provided additional evidence supporting the protective role of various isoforms of apelin, such as apelin-36, apelin-17, and apelin-12, in the context of ischemic stroke. These findings further underscore the significance of the apelin/APJ system in the pathophysiology of ischemic stroke.[21] The neuroprotective properties of apelin extend into its impact on neurodegenerative diseases. Studies have shown that apelin-13 has the ability to alleviate the dopaminergic neurotoxicity induced by 6-hydroxydopamine (6-OHDA), a neurotoxin known for selectively damaging dopaminergic neurons in the animal model of Parkinson's

disease (PD).[22] Apelin could also significantly improve cognitive and motor impairments in PD rats.[23,24] Other studies have pointed out the neuroprotective effects of apelin in animal models of Alzheimer's disease (AD). An illustrative example is the potential of apelin-13 to ameliorate autophagy and apoptosis by modulating the mTOR signaling pathway. This mechanism has been shown to contribute to the improvement of working and spatial memory impairments induced by amyloid-beta (Aβ), a hallmark feature of AD,[25] suggesting its potential as a promising target for AD prevention and treatment.[26]

Besides its impact on neurodegenerative neurological diseases, apelin exerts several behavioral and cognitive effects on mental disorders. Preliminary studies have indicated the presence of apelin and APJ receptor mRNA in brain regions such as the hypothalamus, amygdala, and dentate gyrus, implying that the apelin/APJ system might be involved in the regulation of emotional behaviors.[27,28] In line with this, recent studies have underscored the role of apelin in the amelioration of stress-induced depression-like phenotypes,[29] as well as in reversing the memory impairments following chronic stress.[30]

Given the substantial involvement of the apelin/APJ system in neurological and psychiatric disorders, it is not surprising that its role may extend to the neurobiology of addiction and the underlying mechanisms related to drug response. In the subsequent sections, we highlight current research studies that underscore the potential of the apelin/APJ system within the context of addiction (Figure 1).

Protective effects of apelin against drugs of abuse

Besides its protective properties in various neurological disorders, several studies have suggested that apelin possesses cytoprotective effects against drugs of abuse. Foroughi and colleagues showed that apelin-13 decreased the apoptotic response post-methamphetamine exposure in PC12 cells by increasing cell viability and reducing apoptotic rates. Moreover, apelin could reduce autophagy as well as intracellular reactive oxygen species (ROS) in methamphetamine-exposed cells.[31] These findings indicate that apelin could potentially ameliorate drug-induced neurotoxicity *via* the decrease in oxidative damage, apoptosis, and autophagy cell death. Therefore, apelin could be considered a neuroprotective agent against neurodegeneration caused by psychostimulant drugs.

Alterations in apelin expression have also been reported following morphine dependence. Yildiz et al demonstrated that morphine-dependent rats exhibited a slight increase in apelin gene expression in the hippocampus compared to the control group, suggesting that apelin expression might have been altered to compensate for the neurodegeneration caused by morphine addiction.[32] Similar observations were
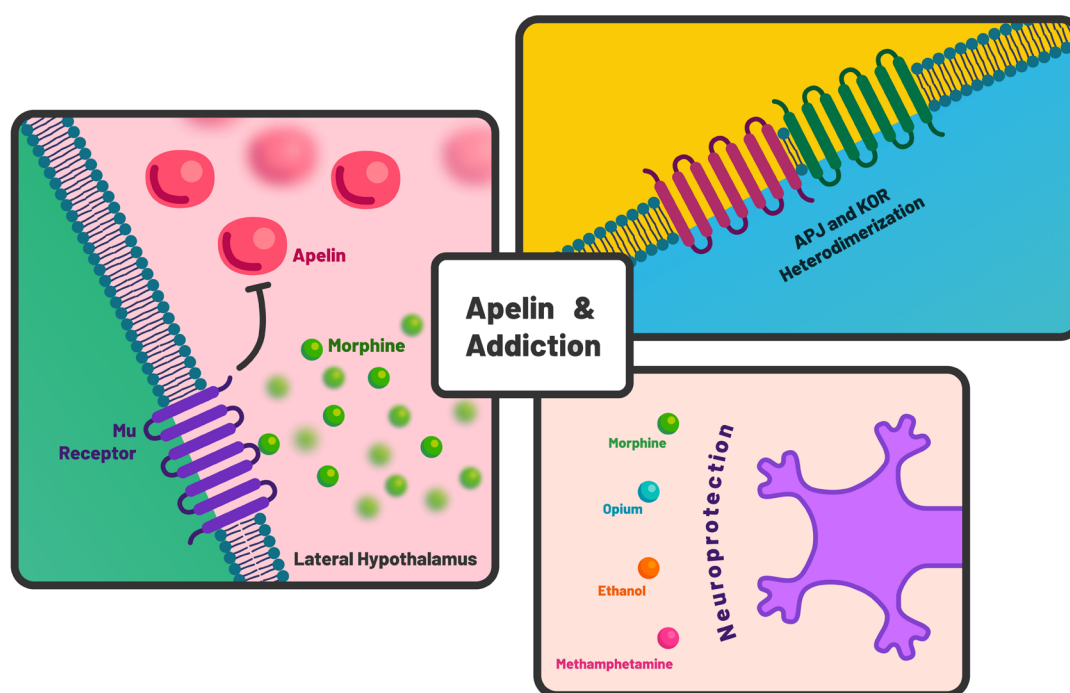
Figure 1. An overview of the potential of apelin/APJ system in addiction. Interaction of mu receptor and apelin in lateral hypothalamus, as well as the heterodimerization of APJ and kappa opioid receptor (KOR), along with neuroprotective effects of apelin against drugs of abuse contribute to its potential involvement in addiction medicine

reported in another study where morphine-dependent rats exhibited significant increases in serum apelin levels compared to their healthy counterparts.[33]

Several studies have also pointed out the neuroprotective effects of apelin on alcohol neurotoxicity. For instance, it has been demonstrated that apelin-13 could significantly alleviate the cognitive impairment and anxiety-like behavior associated with fetal alcohol spectrum disorder in pups of rats exposed to ethanol.[34] Moreover, apelin could significantly increase the brain-derived neurotrophic factor (BDNF) and decrease necrotic cell death induced by alcohol neurotoxicity.[34] In another study, apelin-13 could alleviate ethanol-induced-hippocampal neurotoxicity through anti-oxidative, anti-inflammatory, and anti-apoptotic mechanisms.[35]

The protective effects of apelin in addicted individuals extend beyond its preventive actions against neurotoxicity. For instance, while Tavanai et al reported that opium-addicted patients with acute myocardial infarction did not exhibit altered serum levels of apelin compared to non-addicted patients, they suggested that apelin is associated with the protection of cardiomyocytes in addicted patients.[36] An overview of studies on the protective effects of apelin against drugs of abuse is presented in Table 1. Overall, these findings suggest that apelin might provide clinical utility against the cytotoxicity of abused substances. However, there is a paucity of studies in this field, particularly on other psychostimulant drugs, including cocaine, which warrants further research.

The interplay between APJ and opioid receptors: insights into the potential involvement of apelin/APJ system in addiction

OPRs represent a well-established class of GPCRs that participate in numerous physiological processes within the body. These receptors consist of three primary subtypes: mu, delta, and kappa. Each subtype plays a distinct role in mediating the effects of endogenous opioids and exogenous opioid drugs, thereby influencing pain perception and other related physiological responses, including addictive behavior.[37] There are several findings indicative of the interplay between the apelin/APJ system and opioid signaling, suggesting that this system might be involved in the neurobiology of addiction. Herein, we focus on two opioid-related signalings associated with the apelinergic system that strengthen the possibilities of its involvement in addiction.

Hypothalamic mu receptor signaling and apelin in hedonic homeostasis

The lateral hypothalamus is involved in the regulation of motivated behaviors and serves as a crucial player in modulating reward processes.[38] This hypothalamic region comprises intrinsic neuronal populations that establish connections with reward-related regions, including the ventral tegmental area and nucleus accumbens.[39-41] The activation of lateral hypothalamus neurons contributes significantly to the modulation of the hedonic properties associated with both natural rewarding stimuli and substances of abuse.[42] Research findings have indicated

Table 1. Protective effects of apelin against drugs of abuse

Drug	Type of species	Apelin isoform (dose)	Cytoprotective effects	Reference
Methamphetamine	PC12 cells of rat	Apelin-13 (4 mM)	Reduction of oxidative damage, apoptosis, and autophagy cell death	[31]
Morphine	Male Wistar rats	Hippocampal apelin	Increased expression of apelin in compensation for morphine-induced neurodegeneration	[32]
Morphine	Male Wistar rats	Serum apelin	Significant increase in serum apelin levels of morphine-dependent rats	[33]
Opium	Acute myocardial infarction patients	Serum apelin	Cardioprotective role of apelin in opium addicted patients	[36]
Ethanol	Wistar rats	Apelin-13 (25 and 50 μg)	Amelioration of cognitive impairment and anxiety-like behavior. Increase in BDNF expression and decrease in necrotic cell death	[34]
Ethanol	Wistar rats	Apelin-13 (25 and 50 μg)	Alleviation of spatial memory impairment through anti-oxidative, anti-inflammatory, and anti-apoptotic mechanisms	[35]

that lateral hypothalamus neurons mediate certain aspects of the rewarding effects observed with morphine.[43,44] The mu opioid receptor (MOR) is responsible for generating rewarding effects through direct activation by morphine, as well as indirect activation by various other drugs of abuse, such as tetrahydrocannabinol, nicotine, cocaine, and alcohol.[45-48] Additionally, the MOR can be stimulated by naturally occurring endogenous opioids, leading to rewarding experiences.[49] As a result, this receptor is consistently engaged throughout episodes of drug intake, and excessive stimulation of the MOR probably plays a role in the disruption of reward systems observed in individuals who are dependent on drugs.

It has been demonstrated that chronic stimulation of MORs modifies transcriptional activity within the lateral hypothalamus. Befort et al reported that chronic activation of MOR in the lateral hypothalamus resulted in the downregulation of apelin gene, indicating the potential role of apelin in opioid signaling and hedonic homeostasis.[50] The discovery of decreased apelin transcript levels in the lateral hypothalamus of animals dependent on morphine has two significant implications. Firstly, this observation suggests the potential involvement of apelin peptide in maintaining hedonic homeostasis. Findings of two other studies indicating altered levels of hypothalamic and serum apelin in morphine-dependent rat support this notion.[32,33] Secondly, there is evidence demonstrating the interaction between endogenous opioids of the brain and various peptides, including cholecystokinin and neuropeptide FF.[51] Apelin is now identified as a novel opioid-related neuropeptide and the interaction between this peptide and MOR signaling in the lateral hypothalamus, suggests that it could be involved in the reward system and development of addiction.

Heterodimerization of kappa opioid receptor and APJ: a lead for further investigation

The kappa opioid receptor (KOR) and its endogenous ligands, dynorphins, exhibit widespread expression in the CNS.[52] Upon activation, KOR exerts significant influence on a range of physiological and pharmacological responses, including analgesia, dysphoria, and attenuation of drug-seeking behavior in individuals with substance use disorders.[53] KOR agonists have the ability to inhibit the rewarding effects associated with morphine and psychostimulants like cocaine[54-56]; hence, due to their ability to attenuate the rewarding effects of addictive substances, KOR agonists hold promise as potential therapeutic agents for the treatment of drug abuse. Furthermore, the use of KOR antagonists, such as norbinaltorphimine (nor-BNI) and 5'-guanidinonaltrindole (5'-GNTI) has demonstrated efficacy in alleviating depressive and anxiety-related disorders, which often arise as common withdrawal symptoms and can contribute to relapse in drug use.[57] By targeting the KOR system, these antagonists have shown potential in mitigating these adverse effects and reducing the likelihood of relapse in individuals recovering from substance abuse.[57]

The current understanding of GPCRs has evolved to recognize their existence and functional activity as dimers. It is now widely accepted that GPCRs can form dimers, and emerging evidence suggests the physiological relevance and significance of GPCR heterodimers. Studies have revealed that human APJ forms a heterodimer with KOR resulting in increased protein kinase C and decreased protein kinase A activity.[58] Notably, the apelin/APJ and KOR share similar signaling pathways, most possibly due to their heterodimerization, in various critical cellular processes, including cell proliferation, pain regulation, blood pressure maintenance, and gastrointestinal transit (for review, see [59]). For instance, activation of APJ results in pain modulation through enhanced dynorphins/KOR signaling.[60] Given the close interaction of downstream signaling pathways and the heterodimerization of these two receptors, it is not far-fetched to imagine that the apelin/APJ system may play a role in KOR-mediated actions within the neurobiology of addiction. The extensive distribution of APJ and KOR in neuroanatomical regions involved in the reward system, including the nucleus accumbens, strengthens this hypothesis.[61,62] Indeed, further research is required to elucidate the intricate cross-talk between these systems and their implications in the neurobiology of addiction.

Concluding remarks and future perspectives

Overall, growing evidence suggests that the apelin/APJ

system may have implications for addiction, given its protective effects against drugs of abuse and its interplay with OPRs. The exploration of the apelin/APJ system in addiction opens up exciting avenues for future research. Understanding these mechanisms will not only provide valuable insights into the neurobiology of addiction but may also pave the way for the development of novel therapeutic strategies. Based on the existing evidence on the interplay between the apelin/APJ system and OPRs, further studies are needed to unravel the significance of these interactions in the development of addictive behaviors.

Authors' Contribution
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Writing–review & editing: Mehran Ilaghi.

Competing Interests
The authors declare that no competing and financial interests exist.

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All study protocols were conducted under the approval of the Ethics Committee of Kerman University of Medical Sciences and in accordance with relevant guidelines and regulations.

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