Review Article

The kappa-opioid receptor system in reward function and addiction: an update

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Abstract

Many aspects of human behavior are guided by the reward system of the brain, which is also responsible for mood and motivation. The mood of an individual can affect his feeding, sexual activity and even cognitive processes. Neuropeptide systems in the brain play an important role in regulating mood and drugs of abuse can impact these systems. The dopaminergic system of the brain is a prime player in sensing reward. Kappa opioid receptors and dynorphins are part of the opioid peptide family and influence the brain reward system by modulating dopamine release in the striatum. Kappa-opioid receptor (KOPr) stimulation results in inhibition of dopamine release in the limbic cortical-striatopallidal circuit and can lead to a negative mood state. Drug addiction is a chronic relapsing disorder and addicts typically display a lack of motivation for natural rewards. Drugs of abuse stimulate dopamine release in the nigrostriatal and mesolimbic circuits with concomitant activation of a counter response by the KOPr/dynorphin system. With repeated drug exposure, neuroadaptations in the KOPr/dynorphin system have been found to occur and these can alter the functioning of the system resulting in relapse and neuropsychiatric co-morbidity in addiction. This article takes a look at the role of the kappa-opioid receptor and dynorphins in the brain reward system, the neurobiology of addiction and pharmacotherapeutic implications of the same.

Keywords: addiction, dopamine, dynorphin, kappa-opioid receptor

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Introduction

Many aspects of human behavior are guided by the reward system of the brain, which is also responsible for mood and motivation. The mood of an individual can affect his feeding, sexual activity and even cognitive processes. Neuropeptide systems in the brain play an important role in regulating mood and drugs of abuse can impact these systems.[1]

It is well known that the dopaminergic system of the brain is a prime player in sensing reward and also for establishing stimulus reward associations. Intake of food, intake of drugs and sexual activity have been shown to increase the release of dopamine in the striatum.[1] Many studies have shone the spotlight on the nucleus accumbens (ventral striatum) as reward centre, but the caudate putamen or dorsal striatum, which earlier was thought to be involved in motor control only, also has a critical role here.[1]

Kappa opioid receptors and dynorphin-like peptides influence the brain reward system by modulating dopamine release in the striatum.[1] The object of this article is to examine the role of the kappa-opioid receptor (KOPr) and dynorphins in the brain reward system, the neurobiology of addiction and pharmacotherapeutic implications of the same.

Opioid Receptors and Opioid Peptides

Opioid receptors are widely distributed in the central and peripheral nervous system.[2] In the brain, they were first identified in 1973.[3] Though the opioid receptors first identified were four viz. the mu (μ)-, kappa (κ)-, delta (δ)- and sigma (σ)-opioid receptors,[4] the sigma receptor was later found to be not a receptor[5] and so there were three. ORL1 (opioid receptor like) is a newer opioid receptor.[1] Pharmacological studies suggest the existence of multiple kappa opioid receptor subtypes, but this has not been established.[1] Oprm1, Oprd1, Oprk1 and Oprl1 are the opioid receptor gene family encoding mu, delta, kappa, and the non-opioid orphaninFQ/nociceptin receptors.[3]

The pentapeptides Met- and Leu-enkephalin were the first discovered endogenous ligands for these receptors.[3] Other peptides followed and soon there was an opioid peptide family. The brain opioids are derived from large protein precursor molecules preproenkephalin, preprodynorphin, and proopiomelanocortin and include the melanocortins, endorphins, enkephalins and dynorphins.[3]

Dynorphins and Kappa opioid receptors

The dynorphins are the endogenous ligands for KOPr and are derived from preprodynorphin. Dynorphin A(1-17) was the first to be discovered by Goldstein et al. from porcine pituitary extracts.[6] They found it to be an extremely potent opioid peptide, hence the name dynorphin, from the Greek word dynamis meaning power.[6] Other dynorphins include dynorphin A(1-8), dynorphin B, α-neoendorphin and β-neoendorphin, big dynorphin and leumorphin.[6] Big dynorphin and leumorphin are large forms, dynorphin A(1-8) is the shorter form and dynorphin A, dynorphin B and α-neoendorphin are the intermediate forms.[6] These peptides are stored in large dense core vesicles.[6]

The opioid receptors are present mainly in the limbic system, the brain stem and the cortex[3] and kappa-opioid receptors are, in particular, found in abundance in the basal anterior forebrain, including the claustrum and endopiriform cortex, olfactory tubercle, striatum (caudate putamen and nucleus accumbens), preoptic area, pituitary[3], ventral tegmental area (VTA), substantia nigra, hypothalamus and the amygdala.[1] The dynorphins express great affinity for KOPr and hardly any for the mu and delta receptors, whereas the other opioids show poor affinity for KOPr.[7]

The kappa-opioid receptor is a G protein-coupled transmembrane receptor, acute activation of which leads to inhibition of adenylyl cyclase[1] through (i) potassium channel activation (ii) calcium channel inhibition (iii) inhibition of neurotransmitter release through a Gßγ mechanism.[6] Sustained activation of KOPr leads to activation of mitogen-activated protein kinase (MAPK) pathways.[8]

There is a great degree of overlap in KOPr m-RNA expression sites and binding sites for the dynorphins.[1] However, it has been found that the ventral tegmental area and substantia nigra have higher levels of KOPr mRNA compared to KOPr binding sites suggesting that the KOPr are produced in these areas and then transported to presynaptic terminals in the nucleus accumbens and caudate putamen to control the release of dopamine.[1,3]

The dynorphin/KOPr system, in addition to influencing reward, mood processes and behavior,[2] has several other physiological functions and include analgesic action, fluid

homeostasis[9] and neuroendocrine function as in modulation of the hypothalamic-pituitary axis.[10]

The KOPr/ Dynorphin System and Dopamine Signalling

Dopamine is the neurotransmitter that underpins the reward system of the brain and natural reinforcers like food and sex as well as drugs of abuse stimulate dopamine release in reward areas of the brain such as the ventral tegmental area and the nucleus accumbens.[11] Drug withdrawal, in contrast, results in decreased levels of dopamine in the nucleus accumbens.[1] The dynorphin/kappa opioid receptor system has been postulated to play an important role in modulating dopamine release in the striatum and kappa-opioid receptor agonists (U-50488) have been found to decrease dopamine levels whereas administration of kappa-opioid receptor antagonists (nor-BNI) leads to raised dopamine levels in the nucleus accumbens.[1] Therefore this system inhibits dopamine release in the striatum and plays a pivotal role in the negative feedback mechanism by which dopamine release is regulated.[1]

The limbic cortical-striatopallidal circuit, which includes the mesolimbic dopaminergic system and the nigrostriatal dopaminergic system, plays a major role in the control of mood, motivation, habit and learning.[12] Brain regions comprising this circuit include the prefrontal cortex, VTA, substantia nigra, dorsal striatum and nucleus accumbens (core and shell) as well as the hippocampus, amygdala and ventral pallidum.[13] Dopaminergic afferents arising from the VTA are key elements of this circuit.[9] KOPr and dynorphin peptides are localized in these dopaminergic systems.[2]

The mesolimbic dopaminergic system: There are two groups of neurons in the VTA – one group that projects to the nucleus accumbens (NAc) and another group that projects to the prefrontal cortex.[1,7] Interestingly, the KOPr in the ventral tegmental area have been found to regulate dopamine release in the medial prefrontal cortex but not in the nucleus accumbens; whereas in the nucleus accumbens, dopamine release is regulated by KOPr present on the presynpatic terminals there.[1]

Local or systemic administration of KOPr agonists in the VTA, nucleus accumbens or medial prefrontal cortex results in activation of KOPr in these areas and produces aversive effects.[9] Acute KOPr activation reduces dopamine levels in the mesoaccumbens by two mechanisms: (i) inhibiting release (ii) stimulating reuptake.[9] The resultant decrease in D1 receptor activation is responsible for the aversive effects of KOPr. However repeated exposure leads to downregulation of dopamine transporter (DAT),[9] a membrane-spanning protein that pumps back dopamine from the synaptic space.

The nucleus accumbens consists of 90% GABAergic medium spiny neurons with the remaining 10% being made up of GABAergic, cholinergic, and nitric oxide synthase containing interneurons.[1] Extensive glutamatergic input from the prefrontal cortex, hippocampus and amygdala impinge on the GABAergic neurons and disturbances of glutamatergic and GABAergic transmission in the nucleus accumbens might be responsible for negative mood states.[1]

Some studies have suggested that it is an increase in GABAergic and glutamatergic transmission in the nucleus accumbens that can give rise to negative mood states.[1] However, kappa-opioid receptor agonists which are known to induce negative mood states, have been shown to decrease GABA and glutamate levels in the nucleus accumbens.[14,15] Perhaps there is a complex interaction between dynorphin-like peptides, GABA, and glutamate in the nucleus accumbens in the regulation of brain reward function, which is yet to be worked out.[1]

The **nigrostriatal dopaminergic system:** These are dopaminergic projections to the caudate putamen from the substantia nigra and are known to be involved in locomotion. It is the loss of these neurons that leads to Parkinson's disease and as has been recently postulated, perhaps also to depression.[9]

Dopamine release here is mediated by the dynorphin/kappa opioid receptor system through the release of endogenous dynorphin-like peptides and studies have shown extracellular dopamine levels to decrease following administration of kappa-opioid receptor agonists (U-50488) and increase with the administration of antagonists.[1]

Dynorphin-like peptides attenuate dopamine release by one of two mechanisms: (i) by binding to presynaptic kappa-opioid receptors on dopaminergic terminals (ii) by activating a negative feedback pathway.[1]

The hypocretin/orexin system is composed of neurons projecting to mesolimbic structures from the lateral hypothalamus.[16] Recent evidence indicates that electrical stimulation of the hypothalamus leads to release of both dynorphin and orexin[17] and these peptides act as co-transmitters in the hypothalamus.[18] Dynorphin and orexin have opposing actions within the VTA with orexin stimulating and dynorphin inhibiting the activity of dopaminergic neurons,[18] Most of the cells of the VTA respond to both peptides and thus there appears to be a two-way modulation of reward by dynorphin and orexin in this region.[7]

Endogenous KOPr systems in the ventral and dorsal striatum are tonically active and exert an inhibitory effect on the dopaminergic neurons there. They thus determine the basal level of activity of these neurons and this is known as the basal dopaminergic tone.[9]

Behavioral effects of kappa-opioid receptor agonists

Animal models have been used to study the behavioural effects of kappa-opioid receptor agonists, using various tests like place conditioning tests and the rat forced swim test.[1]

A frequently-used selective and potent KOPr agonist is Salvinorin A, which is is a hallucinogen from the herb Salvia divinorum.[2] In rodents, administration of Salvinorin A, produces anhedonia and depressant-like effects and causes conditioned place aversion while in humans, aversion, dysphoria, sedation and psychotomimesis have been observed.[2]

In humans, kappa-opioid receptor agonist (MR 2033) administration has demonstrated discomfort, anxiety, racing thoughts, severe disturbances in time/space perception, visual hallucinations, depersonalization, even loss of self-control.[1] Certain other kappa-opioid receptor agonists (e.g., enadoline and U-62066) induce visual hallucinations, agitation, sedation, and dysphoria.[1] It therefore appears that a negative mood state is brought on by kappa-opioid receptor agonists both in rodents and humans. However, recent evidence has suggested that KOPr agonists in very low doses may induce positive mood states and high doses may induce negative mood states.[19]

Behavioral effects of kappa-opioid receptor antagonists

Animal models have been used to study the effects of kappa-opioid receptor antagonists (nor-BNI) using tests such as forced swim test, learned helplessness paradigm and the elevated plus maze test and were found to be opposite to those of high doses of agonists.[1] KOPr antagonists have antidepressant-like effects with probable sites of action being the dentate gyrus and CA3 region of the hippocampus, the nucleus accumbens shell and nucleus accumbens core.[1] Anxiolytic-like effects have also been demonstrated.[1]

Kappa-opioid receptor ligands and natural reinforcers

Kappa-opioid receptors have also been found to play an important role in food intake. They increase feeding irrespective of the satiety status and palatability of the food on offer.[1] Site of action is purported to be the medial hypothalamus and the ventral tegmental area.[1] It has been suggested that the emotional state of the animal might have an influence on this increased feeding as mild stressors have been found to increase feeding by decreasing dynorphin-A in the cortex and severe stressors decreased feeding by releasing Corticotropin-releasing factor (CRF), which is known to inhibit food intake.[1] Male sexual behavior is decreased by stimulation of kappa-opioid receptors in the VTA, NAc and the medial preoptic area.[1]

The neurobiology of the KOPr/dynorphin system in addiction

Drug addiction is a chronic disorder with a cyclical relapsing nature characterized by compulsion to seek and take drug(s) uncaring of the harmful consequences/effects that may follow.[20] Addicts typically display a lack of motivation for natural rewards like food and sex that normally drive behavior.[20] Sudden cessation of drug use results in withdrawal signs both psychological (e.g., dysphoria, anxiety, anhedonia, irritability) and physical.[20]

The trajectory of addiction begins with experimentation followed by increasing self-exposure. Then there are periods of withdrawal/abstinence of varying duration, and in susceptible individuals, relapse.[2] The behavioral and neurobiological manifestations in this trajectory may vary depending on the drug of abuse but some downstream effects such as the stimulation of dopamine release in nigrostriatal and mesolimbic circuits and activation of a counter response by the KOPr/dynorphin system are the same for all drug classes.[2] Repeated exposure to drugs of abuse results in neuroadaptations of the KOPr/dynorphin system and reward areas of the brain[20] and this is hypothesized to be the basis of relapse and neuropsychiatric co-morbidity in addiction.[2]

The administration of drugs of abuse results in extracellular dopamine flooding in the mesolimbic and the nigrostriatal dopaminergic systems and a resultant state of euphoria.[1] This increase was found to be 1000% that of baseline levels in the nucleus accumbens (NAc) following amphetamine administration – much higher than that induced by natural reinforcers like food and sex.[1] This drug-induced dopamine release in the nucleus accumbens serves to establish stimulus–reward associations and is thus important in the initiation and maintenance of drug abuse.[20]

Cocaine produces this dopamine rush by binding to and inhibiting the dopamine transporter (DAT).[21] Certain other drugs like morphine stimulate the firing of dopaminergic mesoaccumbal neurons in the VTA.[9]

These high levels are neurotoxic and can lead to the degeneration of dopaminergic terminals in the striatum.[22] It has been found that drugs of abuse also cause dynorphin-like peptides to be released, perhaps as a compensatory mechanism to prevent highly elevated dopamine levels and the concomitant neurotoxicity.[9] However, this increase in dynorphin levels has been observed in the nigrostriatal dopaminergic system but not in the mesolimbic dopaminergic system.[1]

Decrease in dopamine levels are the cause of anhedonic effects following cessation of drug use.[9] However, following prolonged abstinence basal dopamine levels stabilize, but acute exposure to drugs results in greatly enhanced dopaminergic transmission in the nucleus accumbens.[23]

Many studies have implicated the dopaminergic sysem in the changeover from casual use to drug abuse.[9] Following repeated exposure to

cocaine, functional adaptations (some of which are persistent) have been observed in the KOPr/ dynorphin and the dopaminergic systems and these have been hypothesized as being the cause for relapse and neuropsychiatric co-morbidity.[2]

Drugs of abuse alter dopamine release in the prefrontal cortex as well as the NAc and thus gain control over behavioral output.[24] Recent evidence indicates that relapse can be triggered by exposure to stress, stimuli associated with the drug, or the drug itself, acting through the prefrontal cortex as a final common pathway.[9] It is postulated that decreased extracellular dopamine levels and impaired D2 receptor function in the prefrontal cortex may lead to the uncontrollable drug-seeking and lack of drive for natural rewards that is so typical of addiction.[24]

Long term exposure to drugs of abuse brings about enriched prodynorphin (PDYN) gene expression,[9] increased dynorphin mRNA levels[2] and thus an upregulation of the KOPr/dynorphin system as well as alteration in KOPr-activated second messenger signaling in mood and motivation areas of the brain[2] including the dorsal striatal areas, thought to be responsible for compulsive behaviours.[25] And it is this dysregulation of the DYN/KOPr system that has been implicated in the negative mood state associated with drug dependence as well as the drug-craving that occurs in the withdrawal phase.[9] Dynorphin-induced activation of KOPr is responsible for the anhedonia, dysphoria, anxiety, and depression-like states that are brought on by chronic drug exposure.[9]

Individual variation in vulnerability to drug abuse has also been linked to this system.[9] In rodents not previously exposed to drugs of abuse, administration of KOPr antagonist produces very limited effects and it appears that the functional status of the endogenous KOPr/dynorphin system of an individual, also known as endogenous dynorphin tone, (which is normally low) plays an important role in the cyclical nature of addiction and can contribute to exacerbations.[2]

Genetic variations in the PDYN gene can influence the functioning of the dynorphin/KOPr system and cause neurobiological changes which can impact specific stages in the addiction trajectory conferring either relative vulnerability or resilience.[2] It has therefore been hypothesized that high PDYN expression translating into high KOPr/dynorphin tone confers decreased vulnerability in the early stages of addiction trajectory by damping the dopaminergic response to cocaine, whereas in other stages it may increase vulnerability both to the addiction as well as co-morbid psychiatric conditions.[2]

The KOPr system also exhibits gender differences in effects on affective state of individuals.[26] Studies have shown sex-dependent influences on (i) prodynorphin gene polymorphism (ii) Kappa- and mu-opioid receptor heterodimerization and (iii) gonadal hormone regulation of dynorphin release in the spinal cord, hypothalamus and hippocampus.[26] This raises the question of how gender may be an additional factor in addictive behavior. Though sex differences in the KOPr/dynorphin system have not been directly implicated in addiction in humans, animal models have clearly demonstrated sex differences in the effects of KOPr on stress responses and affective states.[26,27]

Pharmacotherapeutic implications

Based on current knowledge of the neuroadaptations in addiction, the KOPr/dynorphin system is a potential target in the treatment of addictive diseases. One of the strategies that could be used in addiction pharmacotherapy might be to decrease KOPr/dynorphin tone so as to minimize the probability and severity of relapse and promote abstinence.[2]

Most patients of drug abuse seek medical help only in the later stages.[2] By then, upregulated dynorphin activation at KOPr results in a negative mood state on withdrawal.[2] However, studies in rats have shown that this upregulated tone decreases spontaneously during intermediate duration withdrawal.[2] A relative blockade of KOPr system by selective KOPr antagonists could serve to accelerate this decrease in tone and may be tried along with other validated treatments for addiction as adjunct therapy.[6]

For prevention of relapse and re-escalation, selective KOPr partial agonists may be tried in view of their role in reward sensing.[2] Chronic KOPr partial agonist treatment is postulated to (i) counter dopaminergic surges due to drug-taking in relapse (ii) prevent excesses and fluctuations in KOPr/dynorphin toneby blocking the effects of endogenous dynorphins.[2]

KOPr antagonists ALKS 5461 and CERC-501 are in Phase-III and Phase-II clinical trials, respectively, for the treatment of treatment-resistant depression (TRD) and their success is being predicted in the near future.[28]

Further research into the KOPr/dynorphin system could lead to the development of novel strategies for treatment of mood disorders, drug addictions, and other disorders of the brain reward system.

Conclusion

The KOPr/dynorphin system plays an important role in modulation of the reward circuitry of the brain and thus influences mood and motivation of an individual. It is implicated in neuroadaptations in addiction trajectory and has therefore emerged as a target in addiction pharmacotherapy. This system is also involved in stress and emotion regulation and has been incriminated in major depressive disorder[28] and a host of other neuropsychiatric conditions such as anxiety and anxiety-related illnesses,[29] and motivational and affective impairment.[30]

However, we are yet to develop a complete and detailed understanding of this system. Much work is still needed to unravel the molecular signaling pathways within this system, its interactions with other neuropeptides and neurotransmitters such as CRF, orexin, serotonin and norepinephrine, and the neuroplasticity effects in different areas of the brain. Further research on dynorphin-like peptides, their receptors and effects will help in working out innovative approaches to treating addictions, mood disorders and associated neuropsychiatric conditions.

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References

1. Bruijnzeel AW. KOPr signaling and brain reward function. Brain Res Rev. 2009 December 11; 62(1): 127-146.
2. Butelman ER, Yuferov V, Kreek MJ. Kappa opioid receptor/dynorphin system: Genetic and pharmacotherapeutic implications for addiction. Trends Neurosci. 2012 October; 35(10): 587-596.
3. Merrer JL, Becker JA, Befort K, Kieffer BL. Reward Processing by the Opioid System in the Brain. Physiol Rev. 2009 Oct; 89(4): 1379-1412.
4. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. Journal of Pharmacology and Experimental Therapeutics 1976; 197:517-532.
5. Hayashi T, Su TP. The Sigma Receptor: Evolution of the Concept in Neuropsychopharmacology. Curr Neuropharmacol. 2005 Oct; 3(4): 267-280.
6. Chavkin C. Dynorphin–Still an Extraordinarily Potent Opioid Peptide. Mol Pharmacol. 2013 April; 83:729-736.
7. Lalanne L, Ayranci G, Kieffer BL and Lutz PE. The kappa opioid receptor: from addiction to depression, and back. Front Psychiatry. 2014 December; 5:170.

8. Bruchas MR, Land BB, and Chavkin C. The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res. 2010;1314:44-55.
9. Shippenberg TS, Zapata A, and Chefer VI. Dynorphin and the Pathophysiology of Drug Addiction. Pharmacol Ther. 2007 November;116(2): 306-321.
10. Bodnar RJ, Klein GE. Endogenous opiates and behavior: 2005. Peptides. 2006 Dec; 27(12):3391-478.
11. Nestler EJ, Carlezon WA Jr.The Mesolimbic Dopamine Reward Circuit in Depression. Biol Psychiatry. 2006;59:1151-1159.
12. Graybiel AM. The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol. 2005 Dec;15(6):638-44.
13. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci. 2005 Nov; 8(11):1481-9.
14. Hjelmstad GO, Fields HL. Kappa opioid receptor inhibition of glutamatergic transmission in the nucleus accumbens shell. J Neurophysiol. 2001;85:1153-1158.
15. Hjelmstad GO, Fields HL. Kappa opioid receptor activation in the nucleus accumbens inhibits glutamate and GABA release through different mechanisms. J Neurophysiol. 2003;89:2389-2395.
16. Thompson AC, Zapata A, Justice JB Jr, Vaughan RA, Sharpe LG, Shippenberg TS. Kappa-opioid receptor activation modifies dopamine uptake in the nucleus accumbens and opposes the effects of cocaine. J Neurosci. 2000; 20(24):9333-40.
17. Li X, Marchant NJ, Shaham Y. Opposing roles of cotransmission of dynorphin and hypocretin on reward and motivation. Proc Natl Acad Sci USA.2014; 111(16):5765-6.
18. Muschamp JW, Hollander JA, Thompson JL, Voren G, Hassinger LC, Onvani S, et al. Hypocretin (orexin) facilitates reward by attenuating the anti reward effects of its co transmitter dynorphin in ventral tegmental area. Proc Natl Acad Sci USA. 2014; 111(16):E1648-55.
19. Braida D, Limonta V, Capurro V, Fadda P, Rubino T, Mascia P, et al. Involvement of kappa-opioid and endocannabinoid system on Salvinorin A-induced reward. Biol Psychiatry. 2008 Feb 1; 63(3):286-92.
20. Koob GF, Volkow ND. Neurocircuitry of Addiction. Neuropsychopharmacology. 2010 Jan; 35(1): 217-238.
21. Nestler EJ. The Neurobiology of Cocaine Addiction. Sci Pract Perspect. 2005 Dec; 3(1): 4-10.
22. Krasnova IN, Cadet JL. Methamphetamine toxicity and messengers of death. Brain Res Rev. 2009 May;60(2):379-407.
23. Kalivas PW, Duffy P. Time course of extracellular dopamine and behavioral sensitization to cocaine. I. Dopamine axon terminals. J Neurosci. 1993 Jan; 13(1):266-75.
24. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry. 2005 Aug; 162(8):1403-13.
25. Frankel PS, Alburges ME, Bush L, Hanson GR, Kish SJ. Striatal and ventral pallidum dynorphin concentrations are markedly increased in human chronic cocaine users. Neuropharmacology. 2008 July; 55(1): 41-46.
26. Chartoff EH, Mavrikaki M. Sex Differences in Kappa Opioid Receptor Function and Their Potential Impact on Addiction. Front Neurosci. 2015 Dec 16;9:466.
27. Russell SE, Rachlin AB, Smith KL, Muschamp J, Berry L, Zhao Z, etal. Sex differences in sensitivity to the depressive-like effects of the kappa opi- oid receptor agonist u-50488 in rats. Biol Psychiatry. 2014; 76(3):213-22.
28. Li W, Sun H, Chen H, Yang X, Xiao L, Liu R, Shao L, Qiu Z. Major Depressive Disorder and Kappa Opioid Receptor Antagonists. Transl Perioper Pain Med. 2016;1(2):4-16.
29. Crowley NA, Kash TL. Kappa opioid receptor signaling in the brain: Circuitry and implications for treatment. Prog Neuropsychopharmacol Biol Psychiatry. 2015 Oct 1;62:51-60.
30. Drui G, Carnicella S, Carcenac C, Favier M, Bertrand A, Boulet S and Savasta M. Loss of dopaminergic nigrostriatal neurons accounts for the motivational and affective deficits in Parkinson's disease. Mol Psychiatry. 2014 March;19(3):358-367.