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An Insight into the Cellular Mechanisms of Addiction to Psychostimulants

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Abstract

Natural rewards like food, sex etc. are evaluated as pleasurable elements or essential for the survival of a mammal due to the interaction of dopamine (DA) released by ventral tegmental area (VTA) on nucleus accumbens (NAc) and other targets in an interconnected neuronal network in brain called 'reward circuit. Psychostimulants induce prolonged and much greater interaction of DA with its targets and develop the drug related memory in lieu of the memories of natural rewards and induce motor activities required for drug acquisition. Long term potentiation (LTP), a major contributor of synaptic plasticity, occurs in many components of the reward circuit due to both acute and chronic drug exposures, resulting in the morphological changes of neurons that may underlie drug related memory acquisition. Potentiation may occur in VTA DA neurons, medium spiny neurons (MSNs) of NAc, prefrontal cortical (PFC) neurons etc. making the probability that glutamate release from PFC will be increased and VTA DA neurons and MSNs will more effectively interact with the released glutamate. The overall result is that ventral pallidum (VP), the main executor of motor behavior, will be disinhibited for initiating motor action via the inhibition of NAc. Finally a situation may arrive when merely a cue associated with the drug used can provoke a subject to seek drug possibly via gluamatergic action of potentiated PFC on NAc. Relapse of psychostimulant seeking behavior after a prolonged withdrawal is mediated by the potentiation of amygdala (Ag) and PFC also contributes to it.

Keywords: Dopamine; Long term potentiating; Medium spiny neurons; Nucleus accumbens; Prefrontal cortex; Psychostimulants; Reward circuit; Ventral pallidum; Ventral tegmental area

Introduction

Addiction can be regarded as the continued involvement of an individual with a drug in spite of knowing negative consequences associated with it [1]. Psychostimulants like cocaine, amphetamine, methamphetamine, methylphenidate and ecstasy are capable of improving mood and relieving anxiety and some of these can make the feeling of euphoria [2-4]. The drugs produce quick rewarding effects and induce craving and relapse of drug seeking behavior after a period of abstinence [5-7]. Abuses of psychostimulants give rise to serious health and social problems and unfortunately any effective medications for the treatment of addiction of these drugs is still lacking [7].

Addiction is considered as a pathological and powerful form of learned behaviour [8]. Synaptic plasticity plays an important role in learning and memory formation. It modifies the efficacy of synaptic transmission at synapses by changing the synaptic organizations and making new synaptic connections [9-11]. Similarly, a number of neuroplastic alterations has been identified many brain regions which seem to be related to the development of addictive behavior [12]. The neural circuits of our brain that enable us to learn and adapt to rewarding environmental stimuli such as for food and sex etc. are strongly challenged and modified by the drugs [13,14]. As a result, neuropathology of addiction arises in the same neural circuit that responds to natural rewards [12]. Addiction thus emerges as a new behavior that only aims to obtain drug rewards at the expense of behaviors that seek natural rewards.

The 'reward circuit' denotes the mesolimbic system [15] that includes by ventral tegmental area (VTA) located close to the midline on the floor of the midbrain [16] and comprises dopamine (DA) neurons that project to nucleus accumbens (NAc), amygdala (Ag), hippocampus (H) and to prefrontal cortex (PFC) etc. [17]. Rewarding effect of addictive drugs including psychostimulants refers to their ability to increase the release of DA by VTA neurons onto NAc so that the behaviours required to obtain the drugs are more likely to be repeated [1,18]. VTA DA neuron projections to other fore brain regions such as PFC and Ag are also important in shaping the drug taking behavior [1]. In addition of obtaining DA via dopaminergic projections from VTA, NAc is also innervated by glutamatergic projections from limbic and cortical areas and the interactions of this released glutamate with NAc are regulated by DA [19]. Finally projection from NAc to ventral pallidum (VP) is responsible for the motor execution of behaviors to achieve the reward [20].

Within the VTA/NAc circuit, DA is released in response to rewarding natural stimuli such as food and sex as well as due to the consumption of addictive drugs [21]. As both addictive drugs and natural rewards stimulate the release of DA in the NAc and other fore brain structures, addictive drugs mimic the effects of natural rewards [22-24]. However, the release of DA induced by addictive drugs supersedes the DA release by natural stimuli both in amount and duration [13]. Since DA has been implicated in reward related learning [25], DA released under the influence of abusive drugs block the natural learning and facilitates learning related to drugs used. Through this aberrant learning mechanism drugs can hijack the reward circuit to induce abnormal forms of synaptic plasticity that may induce persistent drug-seeking behaviors [26]. Thus addiction can be viewed as a form of pathological learning.

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Animal Models for the Development of Psychostimulant Addictive Behaviours

Behavioral sensitization is the progressive enhancement of specific behavioral responses of a species during repeated drug administration that persists even after long periods of withdrawal [19]. The increased behavioral responses result as a consequence of neurobiological changes that reflects drug induced neuroplastic alterations in brain reward circuitry [27]. Locomotor sensitization in rodents serves as a useful model to study the development of addiction [28] which is best characterized for the psychostimulants like cocaine and amphetamine [29] but can also be observed with other drugs [30]. The phenomenon of sensitization exhibits context dependence [31,32] as it has been seen that a rat in which amphetamine was injected intermittently in a novel test cage instead of its home cage, exhibited enhanced sensitized locomotor behavior in response to a challenge dose given in the test cage than in the home cage. Sensitization is also long lived as it has been observed to reappear over a year in rats following the termination of amphetamine administration [33]. These two characteristics of sensitization in rodents has well been noted in human addicts also as cues such as people, places or paraphernalia associated with previous drug use increase the risk of relapse in human addicts after a period of abstinence [15]. Thus owing to have properties like context dependence and persistence, sensitization has been considered as the central neural mechanism underlying the development of addiction of abusive drugs [34].

The reinstatement of drug-seeking behavior in rats is a popular model of relapse in human addicts [35]. In this model, rats can be initially trained to self-administer drugs by pressing a lever for an intravenous drug infusion. After this behavior is being eliminated by extinction training (physiological saline solution is provided instead of the drug to diminish lever pressing activity gradually in the following days), rats reinitiate drug seeking behavior (lever pressing) in response to an acute exposure to the drug or cues previously associated with the self-administration of the drug. As drug cues and drug re-exposure has also shown to play a role in eliciting craving and relapse in human subjects [35,36] the understanding of molecular details of rodent model of reinstatement can facilitate the development of therapeutic strategies against the relapse of drug-taking behaviour in human. .

Synaptic Plasticity and Its Contribution to the Learning of Addictive Behaviors

Synaptic plasticity in brain, a possible substrate for learning, has been documented also in neural reward circuit and may contribute to the learning of addictive behaviors [37]. Synaptic plasticity involves the changes in the strength of existing synaptic connections and may lead to synapse formation or elimination and remodeling of the structure of dendrites and axons [38]. A well-known candidate mechanism for changing synaptic strength is Long-term potentiation (LTP) that enhances in signal transmission between two neurons [39] and can lead to the reorganization of neural circuitry by altering gene and protein expression in them [1]. LTP also occurs in the VTA [40] and other regions in the reward circuit [41,42] as a consequence of behavioral sensitization induced by psychostimulants. Thus it can be speculated that molecular details LTP generation in the reward circuit during sensitization may provide an insight into the development of drug addiction at the cellular level.

Psychostimulant Induced Adaptive Changes in the Components of Reward Circuit Contributing To Addiction

Adaptive changes in the VTA

Normally, the DA transporters (DAT) in the presynaptic membrane of DA secreting neurons terminate DA signaling by removing the transmitter from synapses and returning them into the presynaptic neurons [43]. However, cocaine blocks DAT preventing reuptake of DA from the synaptic cleft [44] and amphetamine either inhibits DA uptake or induces reverse transport of DA through the DAT molecules into the synaptic cleft [45]. Thus due to the exposure of a psychostimulant, a very high concentration of DA is accumulated in the synapses that do not occur in response to a natural reward stimulus. As activities of VTA DA neurons are driven by glutamate [46], it is expected that strengthening the glutamatergic synapses onto VTA dopaminergic neurons will augment their activities and thereby increase DA release into the targets like NAc, PFC etc. The increased degree of interactions of DA at its targets may cause synaptic reorganization or rewiring of the brain reward circuitry [47].

Enhancement of VTA glumatergic excitatory synaptic transmission induced by acute cocaine administration is N-methyl-D-aspartate receptor (NMDAR) dependent that correlates with the initial phase of behavioral sensitization [40]. However, its expression i.e., enhancement of behavioral effects is contributed by the synaptic insertion of new α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid receptors (AMPARs), another type of ionotropic glutamate receptor [48]. This early enhancement of NMDAR mediated excitatory transmission has been found experimentally to be associated with the activation of D5 receptor (a member of D1-like family of DA receptor (DAR)) on VTA DA neuron membrane as cocaine increases extracellular dopamine concentration [47,49-51]. Activation of this receptor, through a sequence of events led to the increased expression of NR2B subunit containing NMDARs on VTA DA neuron surface enabling their enhanced excitatory transmission [28,52-55].

Although acute cocaine administration caused potentiation in NMDARs in VTA DA neurons as early as within 15-20 minutes after *in vivo* injection in rats, the site of synaptic potentiation in VTA DA neurons later shifts to AMPARs [43]. The time of onset of such enhancement of AMPAR mediated transmission has been found to be within 3-5 hours after acute cocaine administration and may last for many days [40,47,56]. This delayed development and persistence of AMPAR potentiation in excitatory synapses in VTA is associated with new protein synthesis as it happens in the late phase of LTP in hippocampus which is thought to underlie mammalian memory formation [57-59]. The reason for such potentiation of AMPARs is due to the changes in subunit composition of this receptor which in potentiated state contains GluR 1/3 subunits in its tetrameric structure instead of GluR 2 subunit (47). This subunit switch allowed calcium entry into VTA DA cells and facilitated LTP generation in them. The LTP generated by calcium in VTA in this case may be independent of NMDAR activation as it has been found that initial activation of NMDARs in some brain regions of rodents facilitate the delivery of calcium permeable and GluR2-lacking AMPARs to the synapses to produce this type of novel LTP [60]. Ultrastructutal studies have also shown that acute cocaine administration in mice causes trafficking of GluR1-containing AMPA receptors on VTA neuronal surfaces [61]. Overexpression of GLUR1/3 in VTA DA neuron and the resultant increase in number of synaptic calcium permeable AMPARs is

believed to have important roles in the development of behavioral sensitization [62]. It can be hypothesized that excessive calcium entry through GluR1containing AMPARs is responsible for the long lasting synaptic potentiation in VTA DA neurons that was observed 3-5 hours following cocaine exposure in rats. As acute cocaine administration induces surface expression of GluR1 in VTA DA neurons, it is probable that the enhanced behavioral responses during cocaine sensitization result from the potentiated transmission through this type of AMPARs. Possibly the augmented potentiation of these glutamatergic receptors causes enhanced activities of VTA DA cells those will release more DA in its targets to make the reward circuit more active facilitating the behavioral expressions of sensitization .

Adaptive changes in PFC

The firing activities of VTA DA neurons and addictive behaviors of the animals are controlled by glumatergic inputs from PFC. Thus strengthening of inputs from PFC to VTA may play an important role in the development of behavioral sensitization [63]. Cocaine increases local DA concentration in brain areas receiving dopoaminergic inputs and it has been reported that due to repeated cocaine administration DA activates DARs in PFC pyramidal cells and promotes LTP generation in them [41]. PFC interacts with NAc by direct glutamatergic projections [64]. PFC also activate VTA DA secreting cells directly by glutamatergic projection but these DA cells do not synapse onto NAc but project back to PFC [65]. PFC neurons may project to and stimulate other brain structure like pedunculopontine tegmental nucleus (PPN) that in turn project to activate specific VTA DA neurons which synapse and release DA in NAc [66]. Ultra-structural evidences in primates have shown the existence of synapse between glutamate-enriched terminal from PPN and midbrain dopaminergic cells [66] and indeed activation of PPN increases VTA DA neuron activities and raise extracellular DA level in NAc [67]. Thus it can be speculated that potentiated PFC neurons will release glutamate in some VTA DA cells which will be stimulated to release more DA in PFC augmenting their excitation. The potentiated PFC neurons can stimulate PPN which in turn will activate specific VTA DA neurons to release DA in the NAc with subsequent augmented behavioral response.

LTP generation in PFC is mediated by a number of ways. In one way, the accumulation of DA in PFC and its interaction with D1 receptors on PFC neurons activates stimulatory G proteins that stimulate PKA which in turn causes the phosphorylation of α1 subunit of $GABA_A$ receptor ($GABA_AR$) that ultimately suppresses the membrane expression of this receptor. This reduced expression of $GABA_AR$ in PFC neuronal membranes reduces the responsiveness of these cells to GABA and facilitates LTP in them by minimizing the entry of negatively charged chloride ions inside [41]. LTP generation in PFC can also be facilitated by the insertion of new GluR1 containing AMPARs in their synaptic membrane via D1 receptor (D1R) stimulation and subsequent PKA dependent phosphorylation of GluR1. These phosphorylated GluR1 can be escorted to the synapses as a consequence of calcium/calmodulin dependent protein kinase II (CaMKII) activation mediated by NMDAR excitatory transmission following D1R stimulation [68].

Psychostimulant Induced Adaptive Changes in NAc

Activities of neurons in VTA are crucial for induction of psychostimulant sensitization but NAc is essential for its behavioral expression [69]. This hypothesis is based on the fact that rats which received repeated doses of amphetamine in the VTA exhibited potentiated locomotor activities in response to peripheral or intra-accumbal exposure of amphetamine [70]. In contrast, repeated administration of amphetamine into NAc increased locomotor activity but could not sensitize locomotor activities in response to systemic amphetamine administration [71]. The major cell type in the NAc is the gamma-aminobutyric acid (GABA) secreting medium spiny neurons (MSNs) which inhibit the cells in ventral pallidum and receives excitatory inputs from H, Ag and PFC etc. [8]. Glutamatergic projection from PFC form synapse onto the head of dendritic spines of MSNs while dopaminergic axons synapse onto their necks [72]. Therefore dendritic spines in MSNs represent the common cellular area where both dopaminergic and glutamatergic transmission could be integrated. The major output target of NAc is VP and this brain structure is the main executor of reward related motor activities. GABA secreted by MSNs of NAc tonically inhibits the cells in VP. This tonic inhibition of VP is withdrawn by the action of DA on dopamine D2 receptors on the GABAergic cells that inhibits them and brings about the stimulus for reward related motor activities [71,73].

In psychostimulant-sensitized animals D1 receptor super-sensitivity occurs in the MSNs innervating the ventral pallidum [69]. DA released due to both acute and repeated cocaine exposure can stimulate D1-receptors in NAc neurons which via the stimulation of G-proteins activate Protein kinase A (PKA) [69,74]. Activated PKA phosphorylate the transcription factor cAMP response element binding protein (CREB) that causes the expression of immediate early genes ΔFosB, a transcription factor is coded by an early gene *fosB* [75,76]. Repeated administration of cocaine causes the accumulation of modified and stable isoforms of ΔFos B (molecular mass 35–37 kDa) in the dynorphin/substance P containing MSNs of NAc. These isoforms interact with the transcription factor JunD to form an active and long lasting transcription factor complex Activator protein-1(AP-1) that bind to AP-1 site of the promoters of certain genes such as the gene for GluR2 subunit of AMPAR for its expression [76,77]. As AMPARs containing GluR2 show reduced calcium permeability, it leads to reduced excitability of neurons [78]. Thus it can be speculated that inhibition of NAc neurons due to increased surface expression of GluR2 mediated by AP-1 disinhibit VP and stimulate sensitized motor activities [71].

The neural adaptations in NAc, just discussed suggest the mechanisms of development of addiction and sensitization that depends only on repeated drug exposure. However, it is mentioned earlier that there is another form of sensitization which is associated with context and is important in cue induced relapse of drug taking behavior. Expression of context-dependent sensitization seems to depend on augmentation of glutamatergic activity in the projection from the PFC to the NAc [79]. PFC has been designated as one of the sites associated with the learning of new context dependent behaviors [80]. Since repeated cocaine exposure generates LTP in PFC pyramidal cells [41], it can be hypothesized that memory of contexts can stimulate the potentiated PFC cells to liberate glutamate in NAc and this glutamate possibly causes the sensitized motor response in animals. NAc is a site of complex assemblage of neurons which mediate drug reward by the inhibition of one MSN subpopulation, while another MSN subpopulation will mediate it by virtue of excitations of its neurons [79]. Neuropeptide enkephalin, an endogenous opoid, co-localize with GABA in some NAc projections to VP [81]. Enkephalin is a high affinity ligand for mu-opoids receptors [82] which are located presynaptically on the axon terminals of the NAc neurons those project to VP [83]. Glutamatergic transmission from PFC to enkephalin containing MSNs can cause the co-release of GABA and enkephalin. The released enkephalin can bind to presynaptic MSN mu-opoid receptors which couple to inhibitory G-proteins. These inhibitory

G-proteins upon activation inhibit voltage gated calcium channels (blocking the influx of calcium) and/or activate potassium channels (causing the efflux of potassium) and bring about hyperpolarization of these MSNs thereby [84]. As a result hyperpolarized MSNs become unable to secrete GABA and VP is disinhibited to initiate reward related motor activities. Since repeated cocaine exposure causes LTP in the PFC which is also a site of context memory formation [80], it is possible that in case of human, observation of drug associated contexts such as people, places, paraphernalia etc. may excite the potentiated PFC cells for enhanced glutamate release in enkephalin containing MSNs. Next the NAc-VP circuit can respond in the above mentioned pathway to bring about motor activities related to drug seeking.

Drug Related Memory in Reward Circuit

There are many evidences which support that DA plays important roles in learning, memory development and memory consolidation [85,86]. Since drugs of abuse increase extracellular DA in many brain regions, they may facilitate the consolidation of the memory of the experiences. It is to be noted that the NAc has been directly linked with associative learning for drug-related stimuli [87]. The circuits involved with memory-related aspects of addiction are likely to involve the frontal as well as limbic brain regions [88]. Imaging studies performed during craving induced by drug exposure, video, or recall have demonstrated the activation of brain regions like Ag, H and PFC which are implicated in several forms of memory. It has been postulated that the activation of the hippocampus and amygdala in association with a drug-related context will activate the PFC which in turn will activate DA cells leading to a further increase in the desire of the drug [88]. Long term exposure to psychostimulants increases the number of dendritic branch points and spines of MSNs in NAc and these structural changes have been found to persist for a few months after the last drug exposure [89]. Such neuroplastic changes have been proposed to underlie learning and memory and particularly the changes in spine morphology and its density have been designated as the signatures of learned associations [90].

Craving and Relapse of Psychostimulant Seeking Behavior

Cocaine addiction shows a high incidence of relapse to drug taking behavior that can appear again after prolonged abstinence from drug administration. Relapse to cocaine abuse arises from intense craving that can be triggered by a single-drug taking experience or a drug associated cues [91]. Prevention of relapse is the biggest challenge to successful treatment of psychostimulant addiction. Development of an effective treatment requires proper understanding of the neurobiological substrates of relapse [35]. The reinstatement of drug-seeking behavior in rodents is a popular model of relapse in human addicts. Substantial progresses have been made so far in deciphering the neuroplastic alterations which occur in the reward circuit during the withdrwal period and these alterations may represent fingerprints of relapse of psychostimulant addiction.

Role of NAc in Relapse of Psychostimulant Seeking Behaviors

Cocaine-primed reinstatement of the psychostimulants seeking behavior is found to be associated with a rise in extracellular glutamate levels in the NAc released from PFC [92]. Furthermore, infusion of AMPA into the NAc reinstates cocaine seeking in a dose-dependent manner [93]. These phenomena indicate that interaction of glutamate released from PFC with AMPARs on NAc neurons may play an important role in reinstatement of psychostimulant seeking behavior. Thus the up-regulation of AMPARs during withdrawal period is necessary for their interactions to cortical glutamatergic stimulus arising as result of craving. It has been seen that both cocaine sensitization and reinstatement experiments resulted in gradual increases in the expression of GluR1 subunit of AMPAR in the NAc after a moderate to long (3-45days) period of abstinence [94-96]. As GluR1 containing AMPARs are more calcium permeable [97], their up-regulation in NAc neurons may facilitate their greater interaction with glutamate for reinstatement to occur. The cause of such up-regulation of GluR1 may be due to decreased glutamate transmission onto NAc neurons during cocaine withdrawal and the resultant decreased excitability of NAc neurons might lead to compensatory increase in postsynaptic AMPARs by a phenomenon called synaptic scaling [94]. In this process neurons detect changes in their own firing rates and increase or decrease the accumulation of glutamate receptors at synapses to stabilize their rate of firing [98]. GluR1 overexpression may also be due to CaMKII mediated phosphorylation and transportation of GluR1-containing AMPARs from intracellular compartments to synapses [36]. Yet another possibility of GluR1 up-regulation may be NMDAR dependent. NMDARs shows time dependent increase in their number during prolonged but not during very short period of withdrawal. It is possible that calcium influx through NMDAR can activate Ras/ERK pathway and enhanced ERK activity renders the increased surface expression of GluR1 subunits [95].

Role of PFC in Relapse of Psychostimulant Seeking Behaviors

Animal studies have indicated that the PFC plays an important role in relapse of drug seeking behaviors elicited by drugs, stress and drug-conditioned stimuli [99] and glutamatergic transmission from PFC to NAc is critical for reinstatement of cocaine seeking behavior [100]. Cocaine priming in rodents following the extinction of their drug seeking behavior after repeated cocaine self-administration leads to augmented glutamate release into NAc and subsequent reinstatement of drug taking behavior. Conversely, blockade of glutamate release from PFC by making it hyperpolarized fails to reinstate drug seeking behavior [100]. These findings clearly demonstrate that activation of glutamatergic projections from PFC to the NAc underlies cocaine-primed reinstatement of drug-seeking behavior. Moreover, reinstatement initiated by cocaine microinjection into the PFC can be blocked by inhibiting AMPARs in the NAc which specifies that NAc is the target of the prefrontal glutamatergic pathway for reinstatement of psychostimulant seeking behavior [101]. It can be hypothesized that when cocaine is administered after its prolonged withdrawal potentiated PFC will cause more glutamate release in the NAc MSNs. Since the GluR1 containing AMPARs are increased on medium spiny neurons during long withdrawal period [94,95], further cocaine challenge will provide enhanced glutamate and AMPAR interaction leading to craving and reinitiation of drug seeking behavior. Clinical neuroimaging studies indicated that craving induced by either drugs or drug-related cues is associated with metabolic activation in specific regions of PFC [35]. Thus augmentation of glutamate release from PFC seems to play an important role in the relapse of cocaine seeking behavior. It is probable that development of memory of drug related cues in PFC renders the greater activation of this brain region during memory recall stimulated by the observation of cues and lead to greater release of glutamate in NAc for subsequent vigorous desire for the drug to occur.

Role of Ag in Relapse of Psychostimulant Seeking Behaviors

Abstinent cocaine users when presented with drug-associated cues or drug-related images, activities of their amygdala are increased [102,103]. Two regions of amygdala namely – basolateral amygdala (BLA) and central amygdala (CeA) seems to be essential for establishing drug-cue association and cue induced relapse of cocaine seeking behavior [104-107]. Since BLA, PFC and NAc are interconnected [108,109] it seems possible that cue induced reinstatement of cocaine seeking behavior may require the interaction of these three brain regions. That the BLA plays an important role in cue-induced relapse has been supported by the fact that lesions of the BLA blocked the ability of drug associated stimuli to reinstate behavioral response in animals [106]. The BLA is not only important in reinstatement of drug-seeking, but also for the acquisition and consolidation of cocaine-cue associations as blockade of sodium channel within BLA [110] and blockade of neurotransmitter receptors in this brain region by their antagonists [111-113] disrupted the acquisition of cocaine-cue associations. The acquisition and consolidation of cocaine-cue association in BLA is found to be NMDAR dependent [113] which is in consistence with the mechanism of fear memory development in Ag that also dependents on the activity of this ionotropic glutamate receptor [114,115]. Since BLA sends dense glutamatergic projections to the NAc [116] and NAc projection to VP translate limbic motivational signals into motor activities [71], it is possible that the BLA–NAc circuit plays an important role in mediating cue induced drug-seeking behavior.

Craving for cocaine stimulated by drug related cues incubates over time after withdrawal. This time dependent increase in behavioral response is accompanied with the increase of active phosphorylated form of ERK in CEA but not in BLA and the phosphorylation of ERK requires the prior stimulation of NMDAR. Furthermore inhibition of ERK phosphorylation in CEA but not in BLA decreases cocaine seeking after withdrawal [105]. Thus it seems probable that BLA is involved in general cocaine seeking induced by cues but CEA is critical for reinitiating cocaine seeking behavior in response to cues after withdrawal. It is possible that glutamate is an upstream regulator that contributes to the activation of the CeA -ERK pathway in response to cocaine cues [105]. Since BLA sends glutamatergic projection to CEA [117,118] it is possible that cue-activated BLA cells can release glutamate in CEA to activate CEA-ERK pathway. Glutamate induced activation of NMDARs in CEA can result in increased calcium influx to activate Ras and Ras-Raf-MEK signaling that can ultimately bring about ERK phosphorylation [119]. Although the downstream cellular mechanism of CEA-ERK activation that contribute to incubation of drug craving is not clearly understood, one possible mechanism may involve ERK- mediated increase in neuronal excitability and synaptic transmission in CEA. It is possible that ERK can inactivate certain subunit of voltage gated potassium channels, preventing potassium ions efflux through them. This results in increased CEA neuronal membrane depolarization [120] and it can be hypothesized that this state of depolarization of neurons can make them more responsive to drug related cues.

Discussion

The molecular mechanism of psychostimulant addiction is a complex process that involves synaptic plasticity causing dramatic remodeling of the reward circuit and ultimately seizing the ability of a subject to acquire natural rewards for survival by compulsive drug use. Synaptic plasticity, a possible substrate of learning mediated by LTP is well documented in major components of the reward circuit and possibly these LTPs establish the formation of reward related pathological memories in psychostimulant users. The drug related memories are so strong that they can elicit vigorous craving and compels the subject for reusing the drug even after prolonged abstinence following the exposure to a single drug use or a drug related cue. In addition, prolonged exposure of psychostimulants lead to the morphological changes in neurons in the reward circuit that represent the formation of learned associations. The ability of abusive drugs in increasing the level of DA in the NAc is considered to be crucial for their reinforcing effects [88]. From the aforesaid discussion it is clear that brain regions like VTA, PFC and NAc play in a network to bring about the reinforcing effect of the psychostimulants. Acute psychostimulant exposure causes the initial increase of DA in its target synapses. This initial increase in DA concentration can potentiate the presynaptic VTA DA neurons that may cause to release more DA in its targets like PFC, NAc etc. Due to repeated psychostimulants exposure abnormal high concentrations of DA are accumulated in the targets of VTA DA neuron that may cause adaptive changes in the target cells. Adaptive changes in PFC, like GABAergic transmission inhibition and GluR1 up-regulation, keep these cells in more excited state and via the activation of PPN augment DA release from VTA DA cells. Adaptive changes in NAc MSNs may include overexpression of a modified and stable isoforms of the transcription factor ΔFos B that have self-inhibitory effect on these cells that leads to the disinhibition of VP enabling them to execute reward related motor activities. Although acute psychostimulant administration may cause motor actions, its repeated exposure cause gradual adaptations in MSNs that lead to progressively increased expression of the behavioral motor activities during sensitization. When psychostimulant uses are associated with a specific context, it is possible that a context memory is formed in the PFC. Since the PFC is potentiated during repeated drug exposure, memory recall in response to cues can activate the potentiated PFC. Released glutamate from PFC may act on a specific subset of MSNs in NAc which are then prevented from their GABAergic inhibition of VP to execute drug related motor activities. Although PFC has been implicated in cue-induced craving for drugs, two regions of Ag namely- BLA and CEA are of major importance for cue induced relapse for psychostimulant seeking behaviors. However, out of these two regions of amygdala, CEA is of special interest for its involvement in cue-stimulated relapse of cocaine seeking behavior after a prolonged period of abstinence.

Conclusion

At present there is no effective treatment for psychostimulant abuse which is a serious social and health problem. Although DA antagonists, D1, D2 receptor agonists or partial agonists, GABAR antagonists etc. have been used for treating psychostimulant dependent subjects with some positive outcomes, a thorough understanding of molecular mechanism of psychostimulant abuse will enable scientists in generating long lasting therapies for the prevention of psychostimulant induced addictive behaviors [121].

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