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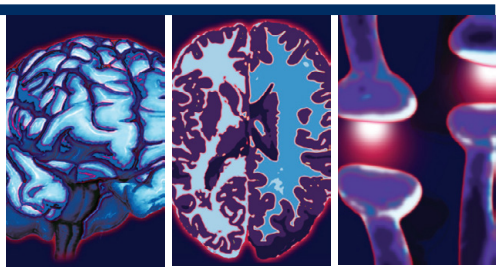

Neuroplasticity-Targeted Therapy Alleviates Severe Addiction

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ABSTRACT

Background

Substance abuse is a dangerous behavior that in some addicts progress from recreational abuse to compulsive drug-seeking and drug-taking behavior. Meanwhile, there would be no evidence to predict this process. Recent studies suggest that following drug abuse some changes occur in the substructure of synapses such as changes in neurotransmitter secretion and their receptors.

Objective

This study is to bring evidence those changes in the substructure of the synapse is necessary for the emergence of uncontrollable addictive substance abuse. Also, proposed targeted treatment for such a problem. Data source: Literature search was conducted in almost all major data indexing databases including Pubmed, Google Scholar and Web of Science. Inclusion criteria: The current study considered all articles with keywords of addiction with all types of neurotransmitters. Then the articles that had designed in such a way that signs of progression of substance use to dangerous abuse were selected.

Results

The result of this study showed that changes in the substructure of synapses such as changes in neurotransmitter release, the release of neurotransmitters in unusual regions and the emergence of unusual neurotransmitter receptors that called changes of neuroplasticity are necessary for the progression of substance abuse to a dangerous addiction. Also, some studies suggested that the application of targeted therapies for such problems is an effective treatment for the prevention of occurrence of a dangerous addiction.

Conclusion

It is concluded targeted therapies for reconstructing and reorganizing such a change not just for one type of neurotransmitter will be helpful for the treatment of addiction.

Limitations

There was a lack of enough human studies.

Keywords

Dopamine, Acetylcholine, Norepinephrine, Serotonin, GABA and Substance P

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Introduction

Drug addiction is the concern of many societies. Addiction is defined as uncontrolled abuse of addictive substance despite negative consequences [1]. The progression of addiction from recreational abuse is a multistage process [2]. In this regard, tolerance is an important intermediary step for progression to the ultimate stage that is called addiction [3]. Reward circuit as composed of Nucleus accumbens, Ventral Tegmental Area (VTA) and prefrontal cortex [4] are the targets of treatment since most abused drugs target this circuit. Synapses in this circuit are the target of addictive substances. Neurons in these areas normally expressed some certain neurotransmitters to keep the pleasure center in a controlled balance [5]. However, after drug abuse, some structural changes, especially in neurotransmitters and receptors, occurs that will disorganize the normal function of the synapses that is called neuroplasticity [6,7]. Therefore the disorganized pleasure center will seek more pleasure [8]. Maybe the brain itself reorganized itself for the loss of normal pleasure. In this sense, the altered release of neurotransmitters and their receptors may eventually predisposed individuals to show uncontrollable addiction. In animal studies for assessing such changes, there is some experiment that shows disorganized pleasure center. For example, Conditioned Place Preference (CCP) can be used to assess the efficacy of the reward center [9] and to find out is the pleasurability of the addictive substance require dopamine or not. In the self-administrator box, the power of substance for establishing addiction compulsive seeking drugs abuse is assessed [10]. In human studies, these changes manifest themselves in the terms of tolerance, abstinence and withdrawal signs [11]. These signs are accompanied by altering neuroplasticity in brain regions that will be fully discussed. Based on these findings it is thought that by controlling the dynamic of synaptic structures the occurrence of abnormal signs will be prevented. These treatments basically are targeted toward reduction of the severity of the abstinence period and improper withdrawal signs. Therefore implementing treatment to reorganize the disorganized synapse may be an effective treatment for the progression of substance abuse. In recent studies, different neurotransmitter has shown to influence the ultimate outcome of drug abuse. Here in this review, we are going to review the possible involvement of different neurotransmitter for the development of addiction and propose new therapies for the prevention and treatment of addiction.

Material and Methods

A literature search was conducted in all major indexing databases including Pubmed, Google, and Web of Science. The included articles were not limited to the time of publication and all relevant articles were used. Also for searching the literature the keywords of addiction with all types of neurotransmitters were used. Then, the abstract was reviewed for investigating the relevance of the study for selecting the proper study. The abstract was selected based on the investigation of proper reward center function that was assessed by Conditioned Place Preference (CCP) and locomotor activity that was considered a sign of intolerance. Also, self-administration was investigated as the sign of the development of dangerous addiction. These signs were considered as the occurrence of dangerous addiction in animal studies. In human studies, valid studies were selected based on the risk of bias. In the case of reporting bias, relevant studies according to the hypothesis of this study were used although there was very few.

■ Synapse structure and function

Electrical synapse: Electrical transmission is mostly mediated by gap junctions [12]. Gap junctions are plaque-like structures that are formed by docked connexins that form pore-like structures in the neuronal membrane that mediates cell to cell ionic current. They are mostly composed of connexin 36 (Cx36) [13]. A recent study suggests that electrical synapses contribute to information processing in the brain. Also, these structures are influenced by neurotransmitter and also by ongoing activity of the neuronal network that is called "activity-dependent plasticity"[14]. For the first time, this phenomenon was described in fish and later on was described Mauthner cells of the auditory system. More studies revealed the presence of electrical synapses in a different structure of the brain that is functional. These structures are influenced by neurotransmitters. Dopamine and glutamate are two known neurotransmitters that change the activity of the neuronal network of electrical synapses [15]. In the retina, inferior olive, thalamic reticular nucleus and anterior hypothalamus [14]. The electrical synapse plasticity is dependent on some factors. The magnitude of electrical coupling can vary

dramatically between different neurons. Also, the plasticity in electrical synapses is regulated by some factors. These factors are an organization based on three-time scales including short-term, intermediate-term and long-term, the balance of protein kinase and phosphatase activities that control phosphorylation state of the connexins, organization of signaling pathways and goal-directed changes to achieve certain outcomes [16]. The brain areas that are related to addiction are encompassed the limbic structures (nucleus accumbens, ventral Tegmental Area) and those that are capable of influencing limbic system structures. Electrical synapse modulation can change the behavior of neurons in these areas [17].

Chemical synapse: Chemical synapses are specialized structures that are located between neurons or maybe other cell types. Information between neurons is mostly translated through chemical synapses. A synapse will be activated by release of neurotransmitter into the synaptic cleft. The synapses are connections between axon and axon, axon and dendrite and axon and cell-body [18]. Neurotransmitters are located inside the vesicles. By the arrival of the action potential, the neurotransmitter will be released into the synaptic cleft that is facilitated by calcium ion. Following stimulation of chemical synapses by neurotransmitters G-protein will be activated and a cascade of events occurs inside the neurons [19].

■ Neuroplasticity reorganization as the consequences of addiction

The recreational effect of addictive drugs mainly arises from the changes in neurotransmitter release that occur in the reward circuit. Addictive drugs mainly affect dopamine release [5]. However, not all aspects of reward such euphoria is related to dopamine release and other neurotransmitters are important in this regard [20]. In the reward circuit, as a consequence of drug abuse, drug-evoked neuroplasticity occurs [21]. Addiction is normally defined as the loss of control over and compulsive use despite negative consequences [22]. So the process that occurs in the reward circuit that eventually leads to addiction is important to consider since proper treatment can be implemented in early stages that may prevent addiction. Here, we are going to overview the changes that occur in reward circuit's members that may show the process that occurs before addiction.

■ Neurotransmitters and mechanisms of action

Since neurotransmitters mainly exert the effect through interaction with ion channels and G-proteins (through cAMP) in synapses, it is useful for knowing the mechanism of this interaction because we use them as therapeutic strategies for treatment of diseases. As will be mentioned in later, different types of neurotransmitters are expressed during addictive substances abuse and in this sense manipulation of these signaling pathways can be used as therapeutic strategies for the prevention of dangerous addiction development. Here, in table 1 it has been given a brief summary of signaling pathways of neurotransmitter that are changed as the consequence of addictive drug abuse [23]. It should be noted that because there are limited studies about subtypes of receptors about the topic of this review, it has been preferred to mention the overall knowledge in this area **(Table 1)**.

Dopamine: Dopamine is the neurotransmitter that in reward circuit that causes euphoria as the consequence of drug abuse [5]. Euphoria as the consequence of Amphetamines is the result of the release of dopamine [24]. From the biological view, dopamine encourages life-sustaining behavior by producing a sense of satisfaction as the consequence of dopamine release [25]. Addictive behaviors mostly produce euphoria by release dopamine in the reward circuit. Following long-term drug administration, dopamine receptors reduce as the consequence of excessive drug abuse. The reduction of dopamine receptors in substantial nigra produces compulsive drug-self administration and also in reward circuit production of enough sense of satisfaction in daily routine life activity reduces [26]. Also, some drugs such as cocaine and amphetamine interfere with dopamine reabsorption in synaptic cleft [27]. It has been suggested not all increased dopamine receptors subtype cause euphoria effects. In nucleus accumbens increased D1 and reduced D2 is associated with euphoric effects [28,29]. Dopamine receptor in other brain areas besides reward circuits' organs is important for drug-related behaviors [30,31]. In one study dopamine, D1 and D2 receptors antagonist in caudate nucleus increased the chance of relapse to drug abuse [32]. The sigma a1 is thought to act through dopamine receptors [33].

Glutamate: Glutamate is considered as the abundant excitatory neurotransmitter in the brain. Recent studies suggest that this neurotransmitter can interfere with the prevalence of addictive behavior [34]. The evidence that supports this theory is the occurrence of locomotor activity following glutamate receptor

Table 1: A brief summary of neurotransmitter receptor types and signaling pathway.		
Neurotransmitter	**Types of receptors**	**Mechanism of action**
Dopamine	D1-like (D1 and D5) and D2-like (D2-D4) receptors	cAMP-dependent and independent
Glutamate	NMDA, Kainate, AMPA and mGlu	Inotropic and metabotropic
Serotonin	5-HTs (5-HP1-5-HT5)	cAMP and Na and K ligand-gated
GABA	GABA-A and GABA-B	Inotropic and cAMP
Norepinephrine	α and β adrenergic receptors	cAMP
Acetylcholine	Muscarinic (m) and nicotinic (n) receptors	Inotropic (n) and metabotropic (m)
Substance P	NKs	cAMP

stimulation [35,36]. However, later evidence suggests that not just in reward circuit, but also in other brain areas such as dorsal striatum [37], Nucleus accumbens [38], septum [39], ventral pallidum [40], and cerebellum [41] addictive substance can result in the release of glutamate. Also, all drugs cannot induce locomotor activity by targeting one specific brain region. For example, caffeine as an antagonist of NMDA receptors in nucleus accumbens cannot induce locomotor activity [35]. During abstinence from an addictive substance such as cocaine glutamate will be reduced in nucleus accumbens [42] but increased in the prefrontal cortex [43]. Also in a recent study, it has been proposed blockage of glutamate receptors in prelimbic areas attenuate the reinforcing of morphine [44]. Different types of glutamate receptors response to the addictive substance. For example, AMPA receptors in nucleus accumbens reinstate addictive substance-seeking behaviors [45] and reverse will occur by antagonist injection [46].

Serotonin: Serotonin or 5-hydroxytryptamine is a monoamine neurotransmitter that is thought to produce a sense of happiness. Recent studies suggest that this neurotransmitter metabolism can be changed by abused drugs [47]. In fact, serotonin has an inhibitory role in the brain [48]. However, recent studies suggest that administration of addictive substances such as morphine can result in a change in the function of serotonin in the brain. The hallucinogen LSD (Lysergic acid diamide) is a direct agonist of serotonin receptors [49]. In chronically morphine-addicted rats induction of serotonin and adrenergic autoantibodies will result in abstinence symptoms [50]. Morphine tolerance can be associated with the expression of 5HT-1 and 5HT-2 in cortical areas of the brain [51].

Gamma-aminobutyric acid (GABA): GABA is considered as the abundant inhibitory neurotransmitter in the brain and recent studies suggest that this neurotransmitter can modulate addictive behaviors. The evidence that supports the role of this neurotransmitter in addictive behavior stems from the evidence that shows cocaine inhibits GABA release in VTA [52]. It has been suggested that GABA that release from interneurons of VTA can modulate the activity of dopaminergic neurons [53]. Based on this study it will be suggested that GABA cannot independently affect addictive behavior that just is influencing the reward circuit can alter the occurrence of addictive behavior.

Norepinephrine (NE): Norepinephrine is considered as one of the most important neurotransmitters that have the multifunctional role in brain especially locus coeruleus [54]. However, in drug abuse studies, recent advances suggest this neurotransmitter can be involved in the regulation of reward circuit [55]. Advances in modeling of animal studies and production of knocked out animal studies have helped researchers very much in this regard [55]. In self-administration paradigm, experiments show that norepinephrine can establish drug self-administration. Experiments with stimulant, morphine, and ethanol showed that norepinephrine can reestablish drug self-administration [56-58]. Experiments have shown that norepinephrine also can cause the emergence of locomotion and sensitization that show the great potential for abusing drugs [59]. Also, experiments with CCP (conditioned place preference) has been introduced NE as the neurotransmitter that can modulate drug-reward properties [60]. It should be noted that drug-related properties of NE are dependent on dopaminergic system interrelations and some aspect is independent of the dopaminergic system. The dependent pathway mainly mediated by stimulation of dopamine release from VTA (Ventral Tegmental Area) and NA (Nucleus Accumbens) with adrenergic neurons of LC (Locus Coeruleus) and brain stem neurons [61-63]. The independent pathway mainly mediated by NE itself [64-66].

Acetylcholine (Ach): Accumulating evidence animal studies suggest a pivotal role for

acetylcholine in drug addiction [67]. Cholinergic neurons are found in some discreet areas in brain and project to other areas and mediate drug-reinforcing properties [68,69]. The progression to addiction mandates some discrete processes. Acetylcholine seems to be involved in these processes. It is well-known that acetylcholine has two types of receptors: nicotinic and muscarinic. ACh through muscarinic receptors in the mesostriatal pathway mediates reinforcement and also neuroadaptation in the striatum [70]. Previous studies have revealed that ACh mediates cocaine self-administration and context-dependent sensitization [59]. Also, ACh has a pivotal role in learning and arousal that are necessary for drug addiction [71]. Experiments have shown that ACh has an important role during recovery from addiction and manipulation of this neurotransmitter helps better recovery.

Substance P: Recent studies suggest that Substance P has an important function in behavioral response to an addictive substance [72]. This altered behavior mainly mediates itself in initiating and maintaining the abusing of drugs. The neurokinin 1 (NK-1) is the receptor of this neuropeptide and most behavioral effects have been attributed to this neuroreceptor. Sensitization as the predictor of potential vulnerability to abusing drugs has been associated with this neurotransmitter but this effect is not direct and it occurs through other neurotransmitters [73-75]. This effect has been mostly been associated with opioids and not cocaine and psychostimulants [76,77].

Neurogenesis: Neurogenesis is defined as the generation of new neurons after birth in some certain brain regions such as hippocampus and subventricular zone [78]. Recent studies suggest that neurogenesis can be considered as a variant of neuroplasticity [79]. Some studies suggest that neurogenesis alternation can influence drug abuse. Recent studies suggest that abusing drugs reduces neurogenesis and as we know reduced neurogenesis can cause a variety of psychiatric disorders [80]. The reduced neurogenesis makes vulnerable individuals to addiction [81]. Also, neurogenesis buffers the stress response and depressive behavior [82]. Alternation of neurotransmitters as the consequences of drug abuse reduces neurogenesis [83]. Overall evidence suggests that reduced neurogenesis as the consequence of drug abuse is important for considering effective treatment.

Results and Discussion

Addictive drugs change the mode of neurotransmitter release and also the mode of receptor expression in various types of neurons especially reward circuit neurons. These changes are associated with altered behavior in animal models addiction. Based on these changes in neurotransmitter release and their receptors new therapeutic approach based on targeting these therapeutic targets. New therapies can be implemented for reduction or increasing of one type of neurotransmitter in a specific brain region and also targeting the receptors and their signaling pathways. However, applying a useful treatment in this regard is not easy because many proposed treatment is just had been applicable to laboratory animal studies and in humans, a few therapies have successfully have used. Here, we are going to recall new therapies that can aim in distant ways for effective treatment. Stem cell therapy as one the variant of cell therapy is an effective treatment in this regard. Other types of cell therapy are not applicable to humans [84]. Also, directed autophagy [85] and synthesizing specific antibodies [86] are very useful. In this regard manipulation of the extracellular environment in stem cell therapy or along is also very useful [87].

Neurogenesis can be increased by application of various strategies. Environmental enrichment, exercise [88], learning [89], electroconvulsive shock [90], chronic administration of antidepressant [91] and other psychotherapies medications. BDNF (Brain-derived Neurotrophic Factor) can increase neurogenesis but in clinical medicine has not been used [92].

Direct targeting of neurotransmitters by antagonists and agonists of receptors that in humans some of them have been used and in some cases, it has been successful, is another effective treatment. Dopamine D-3 receptor has been proposed for the treatment of addiction [93]. Glutamate modulators such as Lamotrigine [94], Gabapentin [95], Topiramate [96], Memantine [97] and baclofen [95] have been used successfully. A number of drugs with no specific known mechanism of function such as Modafinil [98], Acamprosate [99] and N-acetylcysteine [100] have used successfully addicted patients. Studies about Acetylcholine are still are not complete and cannot be used humans [101,102]. GABAergic therapy is a useful treatment for drug-dependent individuals. Agents such as muscimol, bicuculline, and

picrotoxin have used as the drugs that alleviate the burden of addiction [103]. In a recent study serotonin modulators have been proposed as an effective therapy in addiction [104,105]. SSRIs have been proposed for addictive-like behaviors such as gambling [106]. Serotonin has been shown to be effective for interfering with drug-related memories [107]. About norepinephrine and substance P there are no studies to show the usefulness of drug therapy.

Of other types of neuroplasticity-targeted therapies is music therapy that in recent studies it has been suggested that it increases dopamine release [108].

Electrical synapse modulators such as antiepileptic drugs have been used in other brain disorders besides epilepsy such as headaches, Migraine, mood disorders and schizophrenia [109]. If these drugs also can be used in addiction more studies should be operated.

Conclusion

In this review, the neuroplasticity following addictive substance was discussed and it was reviewed the related changes. Based on changes in synapse function new therapies based on changes can be considered. However new progress are still needed for implementing the desired therapeutic strategies. In this regard, more than one type of neurotransmitter can be targeted. Also, other known receptor modulators can be used instead until new progress achieved.

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