Illicit Substances on Dopamine Receptors and Brain

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Drug addiction is characterized by dysregulation of emotional processes involved in motivation and stress patterns. Social and cultural trends also affect and influence processes such as use, addiction, and relapse, as in men and women. The stages of abuse include first use, followed by escalation, addiction with subsequent withdrawal to relapse, which is a common structure for both sexes and is the same for all drugs.

addiction drug abuse neurotransmitter

1. What does Happen in Addicted Human Brain?

Drug and alcohol addiction is classified as a chronic relapsing condition [1][2]. Scientific approaches to addiction are usually based on the premise that addiction is a process that results from changes in the brain due to chronic drug use, which is primarily a social rather than a health problem [3]. The brains of women and men develop in response to genetic and hormonal signals, physical and emotional environment, and individual sociocultural experiences. These components are specified for the individual, but they all participate in brain development throughout life. As a result of biological processes and the complex social environment in which the individual is placed, there are differences in drug addiction by gender, as the brains of men and women differ in one way or another [4]. These differences are due to the response to genetic and hormonal signals, the physical and emotional environment, and individual sociocultural experiences [5]. Four types of gender differences are described: qualitative, quantitative, convergent, and gender differences in the population, which lead to variations in a given trait between men and women. These four types of gender differences operate within each person, and each type of gender difference contributes to the overall phenotype of the individual; the individual types of gender differences can shape the individual phenotype.

2. Drug and Alcohol Use, Addiction and Changes in Brain

Drug use is known to cause significant and lasting changes in brain chemistry and function [6]. The transition from drug experiments to addiction is accompanied by progressive changes in the brain called neuroadaptation [7]. The stages during which addiction develops are three and include intoxication, withdrawal, and preoccupation [7][8]. Neuroadaptation compromises brain function and can lead to a transition from controlled, accidental substance use to chronic substance use. These structural and functional changes of the central nervous system (CNS) promote

and maintain drug addiction and contribute to relapse. Addiction might describe as a recurring cycle with three stages: binge/intoxication, withdrawal/negative effects, and preoccupation/anticipation. Each stage is particularly related to one of the areas of the brain described below [9].

The progression of addiction includes changes in normal brain circuits and long-term pathological and neuroplastic changes that involve critical neurotransmitters such as GABA, glutamate, dopamine, opioid peptides, serotonin, acetylcholine, and neurochains [10]. An example, by potentiating the GABAergic receptors, alcohol inhibits the function of this neurotransmitter and induces continuous stimulation of dopamine. It leads to the production of dopamine in the NAc, which increases the activity of the dopaminergic neurons and leads to desensitization of the reward systems [11].

3. Dopamine Neurotransmission

All addictive drugs activate the mesolimbic dopaminergic system through specific neurobiological schemes. The mechanism included large quantities of dopamine (D) from the dopamine neurons of the ventral tegmental area (VTA). These actions lead to the activation of dopamine neurons by blocking the dopamine transporter effect [12]. In addition, drugs increase the strength of conditioned reactions and the reactivity of stress [8]. Synaptic plasticity is the best-studied neuroadaptation that occurs after exposure to psychostimulants. This occurs at the synapse between two neurons and involves changes in receptor expression, signal transduction, or synapse structure. For example, the use of stimulants, such as cocaine, leads to synaptic rearrangement and possibly altered excitability of dendritic cells due to changes in their morphology [13]. The neurotransmitter dopamine (DA) plays a significant role in the increased sensitization of the stimulatory motivational properties of drugs [14]. Therefore, it is part of the most widely studied neurotransmitter system—dopaminergic. It is a well-established fact that drug use leads to increased dopaminergic transmission in the centers of the brain [15]. During drug intoxication or thirst, the frontal brain areas are activated. It is part of a complex model that includes brain circuits in the nucleus accumbens (NAc) areas, prefrontal cortex [16], amygdala and hippocampus, prefrontal cortex, and cingulate gyrus related to reward, motivation, memory, and cognitive control [17]. Thus, when used, there is an increased mediated response in the striatum and amygdala and weakened activity in the prefrontal cortex. Decreased inhibitory control of the prefrontal cortex to the hyperactive amygdala-striatum system has been observed. The individual cannot self-regulate drug-seeking behavior, which leads to constant and forced use, regardless of the negative consequences [13][18].

3.1. D1- and D2-Like Family of Dopamine Receptors

Brain imaging studies show that addiction is associated with abnormal functioning of the ventromedial cortex, amygdala, striatum, anterior brain, and insular/somatosensory cortex, as well as nonspecific neurotransmitter systems that modulate the activities of neuronal activities involved in decision-making processes [13][19][20]. The results for opiates, ethanol, nicotine, amphetamine, and cocaine show increased concentrations of extracellular dopamine in both zones, but mostly in NAc. PET and fMRI imaging show that cue exposure to cocaine and nicotine administration induces activation of the amygdala region. The reinforcing effect of the drug remains formatted salient stimuli and internally rewarding events, which are due to long-lasting cellular and molecular adaptations.

The stimulation of dopaminergic neurons and increase in glutamate release facilitated the alterations in intracellular processes by increasing or decreasing the synthesis of messenger, transcription, and or structural proteins and mediation of drug-induced sensitization [21][22][23]. Alcohol interacts with the dopaminergic, serotonergic, glutamatergic, and GABAergic neurotransmitter systems in the CNS. In addition, it is responsible for brain modulation and is also present in the reward system. These interactions result in reward, stress effects of circuits reinforcing, and cause changes in neuronal function that underlie the development of alcoholism [11]. Alcohol consumption produces increased levels of DA outside neurons in the ventral tegmental area, and its use discontinuation produces a decreased level of the neurotransmitter, which may contribute to symptoms of alcohol relapse and withdrawal in dependent individuals [24]. For example, the human brain investigation by positron emission tomography (PET) has shown that drug and ethanol intoxication leads to the release of DA and opioid peptides into the ventral striatum area [10][11].

Under normal conditions, the brain maintains a delicate balance between the effects controlled by the dopamine receptors from D1 and D2-like family. Their drug-related activation can lead to stimulation or inhibition of various signaling pathways [25][26][27]. Stimulants cause a rapid increase in extracellular DA levels and supraphysiological activation of the dopamine receptor [28]. Effects caused by cocaine are due not only to DA increase concentration but also to the subsequent stimulation of dopamine D1R and particular D2R receptors. A fast and steep increase in DA levels is associated with activating low-affinity D1R, which are associated with drug rewarding effects, while stimulation of high-affinity D2 receptors is not sufficient for the drug reward effect [10]. The main biochemical mechanism of addiction is due to poor D2R binding and dopamine release in the striatum regardless of the substance [27]. The D1R and D2R are expressed in medium spiny neurons (MSNs) in the striatum, with opposite intracellular effects on cAMP signal transduction [29]. In turn, D1Rs activate the enzymatic activity of adenylyl cyclase and thus alter gene expression, membrane stabilization, and synaptic plasticity [30], and the D2R pathway plays a major role in inducing relapse in cocaine and dominates in cocaine-related signals or stress [31].

4. Neuroplasticity Changes and Other Pathways in Drug and Alcohol Addiction

Serotonin is another neurotransmitter that is involved in the stages of drug abuse and addiction, including cocaine, amphetamines, LSD, and alcohol. Changes in serotonin levels and the serotonin pathway dysregulation are implicated in the pathophysiology of mood and anxiety disorders and can cause not only obsessive-compulsive disorder, anxiety disorders, and depression but drug and alcohol addiction and relapse. The psychostimulants have significant effects on non-dopaminergic mechanisms and monoamine levels such as 5-hydroxytryptamine (5-HT), indicating a role for 5-HT in drug reward. Stimulant administration inhibits monoamine reuptake of serotonergic neurons, elevating extracellular 5-HT in a dose-dependent manner in brain regions NAc, ventral tegmental area, dorsal raphe nucleus, hippocampus, striatum, and cortex. It is known that the acute self-administration of cocaine and other stimulants such as amphetamine and methamphetamine produce acute stimulatory effects on forebrain 5-HT levels. The elevation of the extracellular level of serotonin 5-HT is accompanied by increased activity of the 5-

HT synthesizing enzyme tryptophan hydroxylase in the raphe nucleus and subsequent autoreceptor-mediated inhibition of raphe firing [32].

The gamma-aminobutyric acid system is the third neurotransmitter pathway that is especially important for understanding drug and alcohol addiction. Glutamate is a major excitatory neurotransmitter with a high concentration in brain tissue and plays an important role in amphetamine and its derivatives addiction (ATS). Acute and chronic application of ATS leads to over-activation of the NAc dopamine neurons and can change neural plasticity by change of the functions of multiple members GABA produces in the mesolimbic circuit. The interacting process includes GABAergic interneurons and GABAergic projection neurons and glutamate activation, increased dopamine release through the mesolimbic and mesocortical pathways in the VTA, prefrontal cortex, and striatum to the NAc, which can lead to sustained adaptive and pathological changes in regions with GABAergic neurons and stable drug addictive state [33]. The actions of glutamate are mediated by two kinds of receptors: fast-acting ligand-gated ion channels, which include N-methyl-D-aspartate (NMDA) etc., and slow-acting G-protein (mGlu) receptors. The compensatory glutamate-receptor responses might trigger the DA-receptor adaptations with the potential to affect synaptic plasticity. Activation of these receptors leads to stimulation of intracellular signaling pathways, inducing glutamatergic neurotransmission and drug-induced plasticity. An example of glutamate transmission during drug use (cocaine, nicotine, alcohol, and heroin) is blocking DAT from cocaine, which leads to increased DA levels and activates presynaptic or postsynaptic D1 dopamine receptors. The high concentration of DA can activate postsynaptic D1 receptors and increase NMDA-mediated glutamate signaling by cross-talk between D1 and NMDA receptors [34].

Ethanol increases the GABA by acting on the signal-receiving neuron and facilitates the activity of the GABAA receptor, causing an increase in GABA release in the nucleus accumbens and amygdala. The alcohol acute reinforcing action is carried out by inhibition of glutamate activity in the brain, causing a drop in the extracellular glutamate levels in the striatum. Parallel with this, chronic alcohol exposition can lead to the expression of genes that encode components of the GABAA receptor, which changes the GABAA receptor's function. The increase in the levels of neurosteroids involves allosteric modulation of GABA and changes the excitability of neurons. It is known that glutamate exerts its effects through the NMDA, and high glutamate activity leads to excessive alcohol consumption. The transmission of glutamate is most likely affected due to alterations in the NMDA receptor's functions, and this is involved in changing neuroplasticity [11].

Drug intoxication may be a start point of the neuroplasticity changes that can trigger longer-term molecular neuroadaptations via transcription factors and modify gene expression. Epigenetic remodeling in the brain during drug use involves excessive dopamine signaling, which modulates gene expression and alters the synaptic function and chain activity [35]. In case of long drug use, gene expression can induce changes in the brain and transition to addiction in the vulnerable. Over time, this can be related to maladaptive behaviors in drug abuse individuals. An increasing number of studies have investigated epigenetic alterations, which are a result of drug-induced gene expression changes such as histone modifications, DNA, and miRNAs methylation. For example, administration of morphine can cause histone acetylation and methylation, and DNA methylation, which lead to changes in gene expression. In the phase of cocaine withdrawal, a large number of gene promoters are hyper-

methylated, and after self-administration of the drug, they become hypo-methylated during the reinstatement use stage [36]. In case of chronic exposure to various drugs, activated cAMP/PKA signaling pathway and the up-regulation of a postsynaptic Gs/cAMP/PKA in NAc. An example of critical neuroadaptation is dopamine-mediated cocaine addiction, which promotes escalations of cAMP-dependent protein kinase A (PKA) activity and PKA-dependent protein phosphorylation that modulate the cAMP formation [10]. Fos family proteins (c-Fos, FosB, Fra1, and Fra2) are induced rapidly and transiently in specific brain regions such as the nucleus accumbens and dorsal striatum in acute administration of many drugs of abuse. Chronic drug administration leads to an abnormally and excessively high level of the ΔFosB expression, which characterizes the transcription factor ΔFosB as a sustained molecular trigger for initiating and maintaining an addiction state. It could sustain changes in gene expression and causes increased sensitivity to the behavioral effects of drugs of abuse that persist long after the last drug administration [37]. The repeated exposure to cocaine, amphetamine, morphine, nicotine, phencyclidine and alcohol leads to the accumulation of stable biochemically modified isoforms of ΔFosB within the same brain regions. By dimerization of 35 to 37 kDa isoforms of ΔFosB with JunD has formed an active and long-lasting AP-1 complex and provides drug-induced changes in gene expression for long periods of drug withdrawal in NAc [35].

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