

Understanding the genetics and neurobiological pathways behind addiction (Review)

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Received January 15, 2021; Accepted February 15, 2021

DOI: 10.3892/etm.2021.9976

Abstract. The hypothesis issued by modern medicine states that many diseases known to humans are genetically determined, influenced or not by environmental factors, which is applicable to most psychiatric disorders as well. This article focuses on two pending questions regarding addiction: Why do some individuals become addicted while others do not? along with Is it a learned behavior or is it genetically predefined? Recent data suggest that addiction is more than repeated exposure, it is the synchronicity between intrinsic factors (genotype, sex, age, preexisting addictive disorder, or other mental illness), extrinsic factors (childhood, level of education, socioeconomic status, social support, entourage, drug availability) and the nature of the addictive agent (pharmacokinetics, path of administration, psychoactive properties). The dopamine-mesolimbic motivation-reward-reinforcement cycle remains the most coherent physiological theory in addiction. While the common property of addictive substances is that they are dopamine-agonists, each class has individual mechanisms, pharmacokinetics and psychoactive potentials.

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Key words: addiction, dopamine, reward circuit, genetics, epigenetics, learned behavior

1. Introduction

Substance-related disorders are a set of behavioral, cognitive and physiological phenomena that occur after repeated use of a substance. These typically include: A strong desire to continue using a drug, difficulties in controlling its use, persistence in using it although it has negative consequences, the use of the substance taking precedence over other activities and obligations, along with high tolerance and sometimes withdrawal (1). New developments have altered the way we define addiction. In this sense the Diagnostic and Statistical Manual of Mental Disorders (5th ed.) (DSM-5) (2) has changed the related chapter from 'Substance-Related Disorders' to 'Substance-Related and Addictive Disorders' as well as it lists the following types of substance addictions: Alcohol; caffeine; tobacco; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics and anxiolytics; and stimulants.

Formerly known as an impulse control disorder, gambling was introduced in the category of addictions within the DSM-5. This important change occurred because the pathogenic mechanisms behind gambling are more similar to substance use disorders (2). This approach was initially opposed by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (3), which included pathological gambling to impulse control disorders alongside compulsive sexual disorder, kleptomania, pyromania and intermittent explosive disorder. Introducing gambling disorder to ICD-11 was a point of contention; ultimately the ICD-11 reclassified pathological gambling to gambling disorder and exchanged it from habit and impulse disorders to disorders due to substance use or addictive behaviors. More so, for the first time, gaming disorder was added to disorders due to substance use or addictive behaviors within the ICD-11, a decision challenged by video game producers (4-6).

Although addiction has been classified as a disease since the late 1800s due to its debilitating nature on both the individual and on society, to this day neuroscientists and behavioral scientists have yet to reach a common conclusion on its cause. While neuroscientists seek genetic background and neurological correlates in the reward circuitry that accompany the development of addiction, behavioral scientists, on the other hand, strive to develop and attest behavioral models of addiction (7).

2. Aims and methods

This medical review has proposed the following targets: i) to highlight that addiction has a genetic determinant, which under the influence of both internal factors and external factors, is activated after exposure to addictive agents, giving rise to addiction; ii) to summarize the neurobiological pathways associated with the chronic relapsing seen in addiction-neurotransmitters and reward circuits; and iii) to call attention to the importance of the nature of addictive agents (pharmacokinetics, psychoactive properties) in developing addiction.

We conducted a systematic review by gathering information from PubMed database on the subject of addiction in reference to the aforementioned questions. The selected articles have been published within the last 15 years. The main key words used were: 'Addiction genetics', 'reward system', 'dopamine', 'learned behavior' and 'drugs'.

3. Genetics and epigenetics

Addiction is a multifactorial process and it is difficult to understand why some individuals are more susceptible to developing addictive behavior than others. An individual's background, moral codes and social status determine whether someone may become an addict, but also a person's genetics is one of the most important factors in the development of addiction as far as modern medicine dictates. Heritability is responsible for 40–60% of the population's variability in developing an addiction (8).

There has been proof of both genetic factors that influence the susceptibility of developing an addiction in general, and other genes and sets of genes more specific for one substance or type of addiction (9).

Until genome-wide association studies (GWASs), genetic variant associations were not substantially established. GWASs compare the DNA of individuals that have different phenotypes for a specific trait or medical condition with a control group formed by similar individuals without the disease. Thus, GWASs identify single nucleotide polymorphisms (SNPs), as well as other DNA variants, that are associated with a disease. Unfortunately, SNPs explain only a part of the variance in substance addiction and further research is required. The first GWAS conducted on the subject of addiction was regarding nicotine dependence (10–12).

The relationship between genetic influences and environmental factors took center stage in terms of new findings. It has been pointed out that these two factors can modulate each other (13). For example, one study concluded that genetic influences were decreased in adolescent smoking twins when the parental monitoring increased (11). More so, childhood adversity, stressful life events and lower levels of education seem to have an effect over alcohol-metabolizing, dopaminergic and serotonin transporter genes (9).

Epigenetics studies the heritable changes in phenotype that do not occur after DNA sequence alterations. DNA methylation and modifications of histones are the most studied epigenetic alterations. There are also epigenetic enzymes that mediate DNA demethylation and have important roles in learning, memory, neurodevelopment, but also in some psychiatric and neurologic disorders (14). There are studies regarding

epigenetic changes in the molecular processes that result in addiction to psychostimulants (15,16). Repeated stressful life events are capable of causing epigenetic changes. Given that addicts are individuals with stressful lives, this may explain why these individuals are more vulnerable to neuroplastic changes induced by drugs, changes that constitute the substrate of addiction (17).

Research conducted on mice has emphasized the influence of epigenetic alterations on resilient phenotypes. Thus, in contrast to susceptible mice, resilient ones did not have alterations in the expression of the G9a histone methyltransferase enzyme in their nucleus accumbens when experiencing chronic stress (18).

Furthermore, evidence suggests that maternal conduct can have an epigenetically mediated impact on the offspring's hypothalamic-pituitary-adrenal response to stress (19). Such evidence has been found also regarding the link of paternal stress and increased DNA methylation in the offspring's hippocampus (20).

By identifying the coping styles of resilient individuals and mentoring people at risk for substance use disorder, it is possible to transmit resilient behaviors across generations with the help of epigenetics, in order to gain an important benefit for the population and the health care system.

4. Neurotransmitters

Most known neurotransmitters seem to be involved in addiction in different ways and at different moments.

Dopamine (3,4-dihydroxytyramine). Mounting evidence places the dopaminergic-mesolimbic system as the leading system in the development of addiction, due to its role in encoding motivation and reward (21).

Apart from the motivation-reward-reinforcement cycle, the dopaminergic system plays numerous other roles such as executive functioning and motor planning, sleep and regulation of food intake, neuroendocrine secretion, arousal and sexual gratification. An imbalance in any function may lead to significant disorders. Several neuropsychiatric disorders (Parkinson's disease, Huntington disease, Alzheimer's disease, schizophrenia, bipolar disorder, attention-deficit disorders, Tourette's syndrome) have been associated with a variation in dopamine (22).

Studies have described five types of dopamine receptors: D1, D2, D3, D5, D4 (ordered by density) of the G-protein coupled receptor type. By studying the functioning of these five receptors two subclasses have been characterized: D1-like receptors (D1, D5) and D-2 like receptors (D2, D3, D4). D1-like receptors activate adenylate cyclase, converting ATP to cAMP, in order to disinhibit protein kinase A, which phosphorylates cAMP regulatory element binding protein (CREB). Thus D1-like receptors have a vital role in the regulation of the reward system, learning, and memory. Furthermore, D1 receptors have been linked to various neuropsychiatric disorders, by activating the phospholipase C and inducing intracellular calcium release. In contrast, binding dopamine to D-2 like receptors inhibits adenylate cyclase which decreases the production of cAMP (23).

From a neurophysiological point of view, addiction can be translated as a hypo-dopaminergic dysfunctional state

within the reward circuitry, and therefore is characterized by a decreased in dopamine D2 receptors. Moreover, a greater risk of addiction is associated with the polymorphism of Taq1A (rs1800497), responsible for the number of D2 receptors, the A1 allele having a lower density of D2 receptors (21,24).

Rebalancing dopamine is a difficult objective to reach in order to treat addiction. Using antipsychotics has shown some beneficial results for isolated alcoholism, while in the subpopulation of stimulant users it may aggravate the condition (25).

Serotonin (5-hydroxytryptamine, 5-HT). Available data demonstrate the complex roles of serotonin such as regulating neuroplasticity, cognition and memory, behavior and mood, social behavior and sexual desire, impulse control, as well as appetite, sleep, circadian rhythmicity and neuroendocrine functions (26). Analyzing this assemblage of functions, a simple conclusion can be drawn: Comorbid mood and addictive disorders are expected due to dysregulation of serotonin. When discussing serotonin, 5-HT₂CR (serotonin receptor) cannot be overlooked, as it is recognized as an important nominator in depression, suicide, sexual dysfunction, addiction and obesity (27,28).

5-HT has been linked to addiction by several studies (26,29). Additionally, the serotonergic response is believed to differ from the initial exposure to chronic use, from development of dependence to withdrawal, from abstinence to relapse. For example, during substance intake, 5-HT levels increase which is correlated with a boost in mood while in withdrawal syndrome there is hypoactivity of the serotonin system which may contribute to dysphoria (26-29).

Recent research has examined the role of 5-HT in impulse control, as high levels of impulsivity may be considered a risk factor for the vulnerability to addiction and relapse (29).

Whether to treat the underlying depression, ameliorate withdrawal symptoms, or reduce craving, the efficiency of using antidepressants in addiction disorders is still being debated by physicians. Certain antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), can be used for mood elevation during detox, while bupropion is used to reduce nicotine cravings and ease withdrawal symptoms (29,30).

Endogenous opioids (endorphin, enkephalin). Endogenous opioids are natural pain killers, much like exogenous opioids. Additionally, they control motor activity, intestinal tract motility and peristalsis, the hypothalamic neuroendocrine axis and limbic system regulation of emotional behavioral, modulating euphoric responses and opposing stress (31-33). These effects glorify opioids in substance users. The euphoria together with their highly addictive properties are a recipe for disaster. Endorphins impact addiction via two routes, either by stimulating the mesolimbic dopamine system also independently, by an increase in endorphins in the extracellular space in the nucleus accumbens (34).

Naltrexone, a subtype-nonspecific opioid receptor antagonist, is currently used to treat opioid addiction and alcoholism. Some studies propose naltrexone as a pan-addiction treatment, yet more research is needed (34,35).

Acetylcholine (ACH). The cholinergic system plays a supporting role in encoding motivation alongside dopamine,

but it is also involved in sensory and motor processing, sleep, nociception, mood, stress response, attention, arousal and memory (36).

In regards to addiction, ACH is involved by processing reward, acquisition of conditional associations and conditioned learning, satiation and aversion, drug procurement through arousal and attention. Learning and memory are essential to repeated behaviors (37,38).

Considering its implication, cholinergic medications may represent a potential treatment for addiction but further research is needed. However, AChE inhibitors (donepezil, rivastigmine) can be considered for cognitive impairment associated with long-term substance use (37).

γ-aminobutyric acid (GABA). GABA is the prime inhibitory neurotransmitter; in normal conditions it regulates fear and anxiety. A decrease in cerebral GABA has been linked to schizophrenia, depression, anxiety, addiction and sleep disorders (39).

A decreased activation in the GABA_A receptor induces tolerance when exposed to chronic doses of alcohol, while the GABA_B receptor is involved in adjunct treatments to aid in the initiation of abstinence, maintenance of abstinence, and prevention of cue-related relapse in some addictions (40).

Baclofen, a GABA derivative and GABA_B agonist, has been proposed as treatment for alcohol disorders, yet additional research is warranted (41).

Glutamate. Glutamate is the most substantial excitatory neurotransmitter and is known for the following roles: Synaptic plasticity, cognition, learning and memory, and emotions. Glutamatergic dysfunction has been associated with a series of neuropsychiatric disorders including depression, anxiety, bipolar disorder, schizophrenia and addiction disorder.

Chronic substance use is responsible for plastic changes in glutamatergic response in striatum and midbrain dopamine neurons, intensifying the brain's reactivity to drugs (42).

Ketamine and esketamine are antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor. Preliminary data suggest that ketamine can prolong abstinence from alcohol and heroin as well as reduce the craving for cocaine, but ketamine itself may lead to addiction if used ill-advisedly exceeding the therapeutic dose (43).

5. Reward circuit

The reward system is a collection of brain structures and neural pathways that are responsible for: Associative learning (primarily classical conditioning and operator strengthening); motivation and desire; emotions with a positive value, especially pleasure (44).

The ventral tegmental area (VTA) is the preface of the reward circuit; it is composed mainly of dopamine neurons (60-65%) alongside GABA neurons 30-35% and some glutamatergic neurons (2-3%). To simplify things, dopamine is released by the VTA and is directed toward dopamine receptors (D-1 and D-2 like) established in the nucleus accumbens (NAc) via the mesolimbic pathway, prefrontal cortex (PFC) via the mesocortical pathways as well as other brain regions such as the amygdala and hippocampus. In

this cascade, each cerebral structure plays a complex role in inducing addiction. The nucleus accumbens is a conglomeration of dopamine-sensitive neurons that strongly contributes to the motivation-reward-reinforcement cycle through positive reinforcement and pleasure. The prefrontal cortex plays a complex role in planning action to obtain reward-related substances. The hippocampus is involved in the formation of new memories, in order to remember and seek out pleasurable stimuli. These memories are consolidated with the help of the amygdala, also associated with emotion (44-46).

GABA neurons are vital for processing reward, with similar connections, but opposing effects, GABA activation inhibits dopamine release from the VTA, consequently decreasing dopamine throughout the entire circuit, having a strong role in drug aversion (45).

Dopamine does not act alone; it is influenced by the cholinergic system on three levels: a) VTA: Both receptors (nAChR and mAChR) stimulate the secretion of dopamine; b) NAc: The stimulus that translates into reward is transmitted over an extensive network of neurons between the cortical and subcortical area via cholinergic interneurons; c) PFC: The cholinergic system regulates cognition and conditioned learning setting base for addiction (36,37).

The best example of how the reward circuit functions is based on a legendary study performed on rats, which quickly learn to press a lever to obtain the desired dose of electrical stimulation, pressing the lever thousands of times/hour until exhausted (47). Later on, Goeders and their team allowed rats to self-administer opioids directly into the medial prefrontal increasing dopamine in the nucleus accumbens. In this perspective, animals, like humans, engage in behaviors that increase the release of dopamine (48). The following information will be treated as a new subtitle below (See Point 8 Psychopathology).

6. Addictive agents

Addictive substances act as dopamine-agonists; it is the one common property that ties these agents together otherwise each class has individual mechanisms, pharmacokinetics and psychoactive potentials, which will be treated separately below.

Alcohol. Alcohol addiction is a global burden; therefore, it has been immensely studied throughout the decades. Repeated administration of ethanol is the cause of neurological alteration within the circuits that control motivational processes. This leads to affecting how arousal, reward, and stress are encoded in the brain, creating a vicious cycle. Additionally, chronic use of alcohol induces a change in the aforementioned neurotransmitters leading to sensitization and tolerance.

One neurotransmitter that undergoes change is dopamine. Once acquainted with alcohol, the nucleus accumbens will increase dopamine activity in the anticipation of the substance reinforcing repeated consumption. In reverse, withdrawal produces a decrease in dopamine function, which may contribute to withdrawal symptoms and alcohol relapse (34).

Secondarily, alcoholism affects the expression of GABAA genes resulting in substance tolerance (27,32). Other genes identified that are involved in the metabolism of alcohol are

ADH1B and *ALDH2*, including *GABRA2*, *CHRM2*, *KCNJ6* and *AUTS2*. These genes increase the risk of alcoholism or related traits (49).

Thirdly, a difference in the behavioral responses to stress has been described; alcohol use produces a dysregulation in the hypothalamic-pituitary-adrenal axis (34).

Moreover, alcoholism causes neuroimmune gene induction which alters the limbic system and frontocerebellar neuronal nodes contributing to persistent drinking (50).

Multiple imaging techniques have been utilized to observe the dynamic metabolic changes and imbalance of neurotransmitter accelerating neurodegenerative alteration that occur after chronic exposure to ethanol. Examining the data presented by Sullivan and Pfefferbaum, it was found that both frontal lobe and connective circuitry suffered modifications due to the chronic intake of alcohol (51).

Future research must attempt to fully understand the genetic impact behind alcohol dependency in order to discover genetically tailored treatment for alcoholism.

Tobacco. Nicotine is at the root of tobacco addiction, one of the most abused substances in the world due to its legal status and easy access. Few genetic components have been described in nicotine addiction, especially in adolescent smokers (52). Nicotine binds to nicotinic cholinergic receptors (nAChRs), mediating the complex actions of nicotine in tobacco users. CYP2A6 is responsible for metabolizing nicotine and variability in the metabolic rate contributes to the susceptibility of tobacco dependence, withdrawal symptoms and the risk of lung cancer (53,54). Much like other substances, repeated nicotine exposure alters sensitivity to dopamine within the reward network and circuits involved in learning, stress, and self-control. One particularity of nicotine is that levels peak after 10 sec of inhalation reaching a quicker and faster 'endorphin high' in comparisons to other drugs which translates to frequent cravings and relapses (55).

Electrochemical signaling modifications in the anterior frontal lobe as well as atrophy and neurodegenerative disease have been linked to chronic smoking. In regards to smoking tobacco, a close look to the vascular changes is called for, because the associated decreased cerebral blood perfusion can be a determinant factor in cognitive dysfunction. Moreover, in addition to nicotine, cigarettes contain a multitude of potentially cytotoxic compounds hence singling out a sole cause of atrophy would be challenging (55).

Hallucinogens. Serotonergic hallucinogens or psychedelics are highly psychoactive substances that are associated with perceptual disorders such as hallucinations, complex cognitive symptoms and mood disturbances. The most common representatives from this class are LSD (d-lysergic acid diethylamide), psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine), peyote (mescaline), DMT (dimethyltryptamine), and ayahuasca. The method by which psychedelics function is through binding to serotonin 5-HT_{2A} receptors which is associated with increased cortical glutamate levels. Correspondingly, neuroimaging has demonstrated an increase in prefrontal cortical metabolism. Recreational use of psychedelics is more frequent than addiction although with repeated exposure tolerance sets in rapidly due to downregulation of 5-HT_{2A} receptors (56).

Early studies have sought to use hallucinogens as agonists or partial agonists of 5-HT to alleviate severe forms of depression (57).

Inhalants. Inhalants define a class of substances based on the route of administration (inhalatory or breathing in volatile chemical vapors). Individually, the representatives of this class have different pharmacokinetics. These substances include solvents, aerosol, sprays, gases and nitrites.

Intoxication from acute volatile substances can vary from alcohol-like effects with stimulation or loss of inhibition to intense euphoria and hallucinations, depending on the substance and the dose. Accurate evidence on the effects of chronic inhalant administration is scarce and the results are usually influenced by polydrug use (58).

Dependence on inhalants is often explained by the nature of the substance, the easy availability, the cheap price and the faster onset of effects, yet the neurophysiological and neurochemical aspects need more documentation (59).

Cannabis. Δ 9-tetrahydrocannabinol (THC) is the principal psychoactive component in cannabis; the one responsible for the addictive potential. Available data suggest that THC is a partial agonist of the CB1R (endocannabinoid receptor). Direct effects on the endocannabinoid system and indirect impact on the GABA-ergic, glutamatergic and dopaminergic systems, result in THC producing effects on emotional, executive, memory and reward processing (60).

Cannabidiol (CBD) is also synthesized by the cannabis plant and, in comparison to THC, lacks intoxicating effects, and can offset some of the acute effects of THC. Recent studies suggest it has a positive role in the treatment of epilepsy, addictions, anxiety disorders and psychosis (61,62).

Cannabis plants have become more and more selected to produce THC only in order to maintain consumption.

CB1R is a G protein-coupled receptor that exists in high concentrations in the amygdala, hippocampus, thalamus, cerebellum, basal ganglia and neocortex (especially in the limbic and frontal areas), areas associated with emotional, cognitive and reward processing. Activation of these receptors situated within the central brain reward circuits plays an important role in the pleasurable and anxiolytic effects of the drug. Researchers suggest that THC acts upon reward substrates in a seemingly way as do other abused drugs (60).

There are endogenous lipid-based retrograde neurotransmitters that form the endocannabinoid system which influences the motivation for natural rewards (social interaction, food, sexual activity) and modulates the rewarding effects of addictive drugs. Endocannabinoids bind to the CB1Rs and this leads to suppression in glutamatergic nerve terminals and suppression of inhibition in GABA-ergic nerve terminals. This signaling pathway is disrupted by THC (60).

After THC exposure, impaired salience processing has been observed, a fact that has been explained by the dysregulation of the dopaminergic and endocannabinoid systems that are involved in salience attribution (63).

Research has shown that chronic exposure to THC down-regulates CB1Rs, a fact that explains the tolerance to the rewarding effects of the drug (64). Moreover, there is evidence that CB1R density is restored after one month of abstinence

(except the hippocampus), so not all neurobiological changes are permanent in chronic cannabis users (65,66).

An interest in discovering a link between genetic factors and lifelong cannabis use has increased over time. There is interesting data available on this subject, but further research is needed. An association between rs1800497 Taq1A of the *ANKK1* gene, the gene locus HES7/PER1 on chromosome 17 and cannabis consumption has been found (67), and parental care has also been shown to play an important role (68). More so, depression and self-harm appear to be genetically and phenotypically linked to cannabis use, but the direction of the causality requires further study (69). HTR2B is a major locus associated with cannabis-induced aggression, as it is known that cannabis increases impulsivity and decreases behavioral inhibition (70). The largest genome-wide association study pointed out the significant single nucleotide polymorphism and gene associations in 16 regions. It was shown that the *CHRNA2* gene has a decreased expression in the cerebellum of cannabis-dependent people (71). Other genes associated with lifetime cannabis use are *NCAMI* (implicated in alcohol use, smoking, schizophrenia, mood disorders), *SCOC*, *CADM2* (a synaptic cell adhesion molecule from the immunoglobulin family, linked to risk-taking behavior, alcohol consumption, processing speed) and *KCNT2* (72,73).

Opioids. Even though effective treatment is available for opioid intoxication, relapse is frequent in opioid addicts, mainly due to the opioid receptors' tolerance after repeated use of opioids. After tolerance is developed and the euphoria fades, addicts start feeling symptoms of withdrawal, such as abdominal cramps, diarrhea, sweating, agitation, bone pain, myalgia, and rhinorrhea (74). These withdrawal symptoms develop quickly and can be alleviated by correct treatment.

Opioid receptors are located in the brain, skin, spinal cord, gastrointestinal tract and after stimulation cause euphoria, analgesia, sedation and respiratory depression.

There are three discovered subtypes of opioid receptors: Mu, kappa and delta, with different effects (the common effect is analgesia) and disposition. Mu receptor stimulation produces euphoria, respiratory depression and physical dependence; kappa receptors trigger sedation and dysphoria, while delta receptors stimulate anxiolysis. Mu receptors are crucial for the activation of the reward system (75). An interesting explanation for why adolescents are more predisposed to addictive behaviors in comparison with adults lies in the fact that in this category of patients mu opioid receptors have increased positive reinforcement and less withdrawal symptoms (76).

Studies have concluded that kappa opioid receptors have anti-reward effects in opposition to mu receptors. They are involved in the relapse of addicts, because during the addiction process these receptors are stimulated, leading to dysphoria in withdrawal and abstinence phases, and finally to relapse (77,78).

In order to stave off withdrawal symptoms without consuming more heroin, patients can receive opioid agonist therapy with methadone, buprenorphine or naloxone. Methadone is a full mu opioid receptor, which also has some agonist effects on kappa and delta receptors. Its half-life is longer, causes fewer withdrawal symptoms and helps opioid

addicts have a more stable life. Buprenorphine is a partial mu agonist, partial kappa agonist or functional antagonist, delta agonist and is safer than methadone. Naloxone is an opioid receptor antagonist used for acute opioid intoxications (79).

Researchers have attempted to discover genes linked to opioid addiction and a genome-wide association study discovered SNPs from multiple loci-KCNG2*rs62103177 are connected to opioid dependence (80).

Genes associated with heroin addiction have been classified into two systems: The dopaminergic one and the mu opioid receptor one. In the dopaminergic gene system, the following SNPs are listed: rs1800497, rs1079597, rs4680, rs747302, rs936462, rs1800498, rs1800955, while in the mu opioid receptor gene system, rs7997012, rs1799971 and rs540825 are included (81).

Sedatives, hypnotics, and anxiolytics. Benzodiazepines (BZDs) are the most representative class for this category of drugs. BZDs have been increasingly prescribed by doctors in the last few years, thus BZD abuse and dependence have become a serious medical issue (82).

The calming or sedating effect of BZDs occurs after binding to a specific site on the GABA type A receptors (ligand-gated ion channels), the excitatory neurons are inhibited, the VTA glutaminergic drive is reduced, as well as the nucleus accumbens' dopamine release. The GABA-ergic neurotransmission is modulated by chronic exposure to BZDs, which leads to tolerance, dependence and withdrawal. KB220 is a pro-dopamine regulator, that can be used to produce dopamine homeostasis and combat benzodiazepine use disorder, but future research is needed in this field (83,84).

There have been attempts to discover genetic factors that play a role in BZD addiction. Researchers have investigated the genetic polymorphisms of MAOA (the gene metabolizing catecholamine) and GABA A subunit alpha 2, because of their potential link with anxiety and addiction. The results have been unsatisfactory, as none of the investigated polymorphisms did determine addiction. However, studies revealed some genetic predispositions to personality features. For example, genotype 3/3 MAOA is associated with lack of anxiety and higher extraversion, while genotype 4/4 MAOA was found in individuals with higher levels of introversion and anxiety (85). Given these data, the genetic implication in BZD dependence remains a subject for further exploration.

Stimulants

Cocaine. Cocaine hydrochloride is used especially intranasally, but it can also be administered subcutaneous and intravenous or by smoking crack cocaine. The path of administration is related to the severity of the dependence; therefore higher levels of addiction have been described in injection users, followed by smokers, and lower levels with intranasal users (86). Its effects include euphoria, increased sexual appetite, enhancement of intellectual and physical activity, higher self-esteem and easier social networking, which makes cocaine an attractive substance. It has been linked with high economic status and male to female ratio (87). Like in the case of other substances that cause dependence, environmental risk factors are important in cocaine addiction. Some of those factors include childhood abuse, peer drug use, drug

availability, household drug use and poor social activities (86). Interestingly, parental monitoring is not important for cocaine use (88).

Regarding genetics, research indicates that there is little specific genetic variance for cocaine addiction. One genome-wide association study on cocaine addiction identified an SNP which maps to an intron of the *FAM53B* gene. This gene is believed to be linked with axonal extension during development and cell proliferation (89).

Some research suggests a hereditary factor in cocaine addiction. Several studies regarding the effects of paternal cocaine use on offspring behavior conclude that individuals from the next generation were more likely to consume drugs of abuse (90).

The medical community is awaiting the discovery of an effective treatment for cocaine addiction, such as a cocaine vaccine (91), cocaine hydrolase, or even deep brain stimulation of the nucleus accumbens (92).

Methamphetamine (METH). Although METH is a highly addictive drug, its addiction mechanisms are less studied.

Available data suggest that METH exposure activates neuroinflammatory and neuroplastic processes in the brain, which may lead to parkinsonism (secondary to DA neuron damage), cognitive deficits, depression and promote addiction (93).

Researchers have found important decreases in DA levels, density of dopamine transporters, tyrosine hydroxylase levels in both the striatum and the cortex of METH addicts (94).

More so, imaging studies have shown a reactive astrogliosis inside the brain of METH abusers. The microgliosis has been shown to precede changes in striatal dopamine neurons, thus suggesting that microglial activation is implicated in the development of neurodegeneration (94). Microgliosis was found to persist two years after the beginning of abstinence and has been linked to long-term neurological damage of METH (95).

Studies have aimed to ascertain whether METH addiction can be caused by epigenetically induced alterations in gene expression known to play a role in cognitive functions and synaptic plasticity. It has been found that this drug upregulates several genes that are involved in cell-to-cell signaling and in cAMP response element-binding protein (CREB), such as *GIRK2*, *HCRTR1*, *GABBR2*, and *KCNJ6*. Activation of *GIRK* and *GABBR2* mediate DA neuronal excitability (96).

7. Behavioral addictions

Gambling addiction and gaming disorder are the single two non-substance addiction introduced in the ICD-11. Other behavior addictions yet to be officially recognized by the medical community include food, sex, pornography, shopping, and exercise.

The overexpression of Δ FosB in the nucleus accumbens seems to be present in both behavioral addiction (food, sex, exercise) as well as substance addiction (alcohol, cannabinoids, cocaine, nicotine, and amphetamines) (97). An even closer look shows that gambling disorder and gaming disorder have a similar genetic background known as DRD2 Taq1A1, specifically the Ankk1 mutation (98).

Behavioral addictions follow the same reward patterns as substance use, with the same associated phenomena of craving,

tolerance, relapse and withdrawal (described as anxiety, irritability, and emotional instability) (99).

Gambling disorder (GD). Based on the ICD-11 criteria for gambling disorder (4), gambling disorder is characterized by a pattern of persistent or recurrent gambling behavior, which may be online (i.e., over the internet) or offline, manifested by: i) impaired control over gambling (e.g., onset, frequency, intensity, duration, termination, context); ii) increasing priority given to gambling to the extent that gambling takes precedence over other life interests and daily activities; and iii) continuation or escalation of gambling despite the occurrence of negative consequences.

The behavior pattern is of sufficient severity to result in significant impairment in personal, family, social, educational, occupational or other important areas of functioning. The pattern of gambling behavior may be continuous or episodic and recurrent. The gambling behavior and other features are normally evident over a period of at least 12 months in order for a diagnosis to be assigned, although the required duration may be shortened if all diagnostic requirements are met and symptoms are severe.

The severity of gambling can be predicted with two main personality traits found in gamblers: Harm avoidance and self-directedness. Additionally, the inability to regulate negative emotions has also been associated with a risk of non-strategic gambling (100). Approximately 96% of gambling addicts have overlapped criteria with at least one other psychiatric diagnosis, and 49% have been treated for another mental illness (101). The study of neuroimaging in gamblers shows structural and functional modifications in the reward circuits (102).

Gambling disorder presents 50–60% heritability rates (103). Furthermore, genetic findings were described in gambling disorder such as the associations of the C/C genotype of the serotonin receptor 2A T102C (rs 6313) polymorphism and the PG phenotype (103).

A nuclear medicine tomographic imaging technique (SPECT) found an interesting parallel between psychostimulant drugs such as amphetamines and a motorbike-riding computer game regarding the ventral striatum's dopamine release (104). It is known that video game addiction in adolescence is a disguised form of academic burnout syndrome. Behind the phenomenon there may be disorders of the hormonal balance, of the hypothalamic-pituitary-adrenal axis, connected with disturbances of dopamine levels (105). Moreover, greater activation of orbitofrontal, anterior cingulate, dorsolateral prefrontal and nucleus accumbens was found when World of Warcraft fans who played more than 30 h per week were exposed to game cues, in comparison to those playing less (106).

Genetic research has pointed out the importance of the *CRHR1* gene in gaming addiction (107).

8. Psychopathology

Primary psychiatric disorders that favor addiction must not be confused with psychiatric disorders secondary to the effects of addiction (anxiety, depressive, psychotic disorders, co-addictions).

Based on psychological theories, there are three psychopathological dimensions associated with addictive behaviors:

Alexithymia, depression and the search for sensations. Two vulnerability factors appear to be involved: i) Insecure attachments developed in childhood (especially separation anxiety); ii) Depressive vulnerability—the existence of past depressive experiences without being able to objectify a current depression (108,109).

Drug abusers seek anticipated satisfaction from the used substance creating a vicious cycle. Thus, with consumption the satisfaction is obtained, which has an ‘immediate strengthening power’, leading to habit. Meanwhile it accentuates the feeling of incompetence due to the succession of events. Cognitive and behavioral aspects are responsible for strengthening of the habit (110).

An early approach in intrapsychic dynamics, not doubled by the drug control of withdrawal or craving, will increase the impulsivity and the risk of acting out behaviors. An exclusively pharmacological approach can superficially control symptoms without involving profound changes in internal or inter-relational dynamics. A double approach is recommended for tackling addiction (111).

9. Conclusion

The present analysis suggests that there are genetic traits behind the development of addiction but internal, behavior and external factors are not to be underestimated. The dopamine-mesolimbic motivation-reward-reinforcement cycle remains the most coherent physiological theory in addiction. The common property of addictive substances is that they are dopamine-agonists; otherwise each class has individual mechanisms, pharmacokinetics and psychoactive potentials, reinforcing the importance of the dopamine-mesolimbic system.

Further knowledge on the genetic, epigenetic, and neurobiological bases of addiction will allow specifically targeted medicine, with higher success rates and lower adverse reactions to compliment the psychological approaches that tackle the behavioral problem in order to diminish this worldwide issue.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AP and MM designed and drafted the initial review. AMD gathered the medical information and conducted the final view and structure of the article. AP investigated the present area of research and gathered the important information. RVC finalized the work, analysis the results and approved the final version of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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