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Cassiani-Miranda, Carlos Arturo; Blanco-Palomino, Alexander;
Arismendy-López, Yinneth Andrea; Socarrás-De la hoz, Natalia Marcela
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ARTÍCULO DE REVISIÓN

Etiopathogenesis of drug dependence: an explanatory synthesis from an epigenetic perspective

Etiopatogenia de las drogodependencias: una síntesis explicativa desde una perspectiva epigenética / Etiopatogenia das toxicodependências: uma síntese explicativa a partir de uma perspectiva epigenética

Carlos Arturo Cassiani-Miranda¹, Alexander Blanco-Palomino¹, Yinneth Andrea Arismendy-López¹, Natalia Marcela Socarrás-De la hoz²

ABSTRACT

The use of substances with addictive potential is a relevant health problem. Scientific evidence suggests that the underlying mechanisms that regulate behavioral processes in addictions involve a complex interplay between genetic and environmental factors. Therefore, this narrative review aims to provide a framework to synthesize the evidence on gene-environment-agent interactions from the perspective of the natural history of the disease and the stages of the addictive process for alcohol, nicotine, cannabis, psychostimulants, and opioids. In this review, we conducted an exhaustive literature search without time limits in PubMed, Ebsco, Lilacs, and SciELO, reviewing the title and abstract we selected original articles in humans or animals that addressed the etiology of addictions according to the methodological approach of gene-environment (G-E) interaction, including articles in Spanish, English, and Portuguese. Genetic studies have revealed the critical role of epigenetic modifiers (histone acetylation) in maintaining brain homeostasis in pathological conditions and focusing on G-E interactions will also allow characterizing subgroups (based on environmental factors) at high risk for addictive behaviors that can be targeted for specific interventions. Thus, treatment strategies should encompass a combination of psychosocial interventions with gene therapy involving pharmacological manipulations of histones that may contribute to design better therapies and perhaps lead to more successful management of drug dependencies.

Keywords: etiology; genes; environment; substance-related disorders; epigenomics

RESUMEN

El consumo de sustancias con potencial adictivo es un problema relevante de salud. La evidencia científica sugiere que los mecanismos subyacentes que regulan los procesos comportamentales en las adicciones involucran un complejo interjuego entre factores genéticos y ambientales. Por lo tanto, esta revisión narrativa tiene como objetivo aportar un marco de referencia que permita sintetizar la evidencia sobre interacciones genes- ambiente-agente desde la perspectiva de la historia natural de la enfermedad y los estadios del proceso adictivo para: alcohol, nicotina, cannabis, psicoestimulantes y opioides. En esta revisión realizamos una búsqueda exhaustiva de la literatura sin límites de tiempo en PubMed, Ebsco, Lilacs y SciELO, revisando el título y el resumen se seleccionaron artículos originales en humanos o animales que abordaran la etiología de las adicciones según el enfoque metodológico de interacción entre genes y ambiente (G-A), incluyendo artículos en español, inglés y portugués. Los estudios genéticos han revelado el papel crítico de los modificadores epigenéticos (acetilación de las histonas) en mantener la homeostasis cerebral en condiciones patológicas y enfocarse en las interacciones G-A también permitirá caracterizar subgrupos (basados en los factores

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- 1 Programa de Medicina, Facultad de Ciencias de la Salud, Universidad de Santander (UDES). Santander, Colombia.
- 2 Programa Psiquiatría, Facultad de Medicina, Universidad Nacional de Colombia. Bogotá, Colombia.

Dirección de correspondencia: Carlos Arturo Cassiani Miranda. Correo electrónico: ca.cassiani@mail.udes.edu.co

ambientales) de alto riesgo para conductas adictivas que pueden ser objeto de intervenciones específicas, por lo que, las estrategias de tratamiento deben englobar una combinación de intervenciones psicosociales con terapia génica que involucren las manipulaciones farmacológicas de las histonas que pueden contribuir a diseñar mejores terapias y tal vez conducir a un manejo más exitoso de las drogodependencias.

Palabras clave: etiología; genes; ambiente; trastornos relacionados con sustancias; epigenómica

RESUMO

O consumo de substâncias com potencial viciante é um relevante problema de saúde. Evidências científicas sugerem que os mecanismos subjacentes que regulam os processos comportamentais em vícios envolvem uma interação complexa entre fatores genéticos e ambientais. Portanto, esta revisão narrativa visa fornecer um quadro de referência que permita sintetizar as evidências sobre interações gene-ambiente-agente sob a perspectiva da história natural da doença e as etapas do processo de dependência para: álcool, nicotina, cannabis, psicoestimulantes e opióides. Nesta revisão, realizamos uma busca exhaustiva da literatura sem limites de tempo no PubMed, Ebsco, Lilacs e SciELO, revisando o título e o resumo, foram selecionados artigos originais em humanos ou animais que abordassem a etiologia dos acréscimos de acordo com a abordagem metodológica de interação entre genes e ambiente (GA), incluindo artigos em espanhol, inglês e português. Estudos genéticos revelaram o papel crítico dos modificadores epigenéticos (acetilação de histonas) na manutenção da homeostase cerebral em condições patológicas, e o direcionamento das interações GA também permitirá caracterizar subgrupos (com base em fatores ambientais) de alto risco para comportamentos aditivos que podem ser alvo de ataques específicos. intervenções, portanto, as estratégias de tratamento devem abranger uma combinação de intervenções psicossociais com terapia gênica envolvendo manipulações farmacológicas de histonas que podem contribuir para projetar melhores terapias e talvez levar a um manejo mais bem-sucedido das dependências de drogas.

Palavras-chave: etiologia; genes; ambiente; transtornos relacionados a substâncias; epigenômica

INTRODUCTION

Substance use disorders (SUD) are chronic and debilitating conditions characterized by chronic behavioral disturbances that arise in response to repeated exposure to drugs of abuse in vulnerable individuals¹. SUD are multifactorial phenomena whose etiology involves a complex interplay between genetic and environmental factors². Scientific evidence suggests that the underlying mechanisms that regulate behavioral processes in addictions involve changes in the genetic expression of components of the brain reward circuitry, in particular in the mesolimbic dopaminergic system³.

In the past decade, research has relieved candidate genes^{4,5} involved in addiction risk through genome-wide association studies^{6,7}. Additionally, the crucial role of epigenetic mechanisms^{8,9}, which mediate the enduring effects of drugs of abuse on the brain, has been established through animal^{10,11} and human studies^{12,13}.

A key current research challenge is to delineate how environmental influences interact with genetic factors to facilitate the initiation and persistence of addiction

(SUD)^{2,14}. Genetic and environmental vulnerability to initiate the use of addictive substances has been extensively studied in recent years, but the specific mechanisms of this complex gene-environment interaction are not entirely clear^{9,15} and few studies have evaluated the moderating effect of the genetic load of environmental factors (gene-environment-G-E interactions)^{16,17}. This knowledge gap could limit the ability of recent findings in the field of epigenetic research to translate into advances that specifically impact the understanding, prevention and treatment of addictions¹⁴.

This review aims to provide a framework for synthesizing the evidence on gene-environment-agent interactions from the perspective of the natural history of the disease and the stages of the addictive process for alcohol, nicotine, cannabis, psychostimulants, and opioids. Initially, evidence on studies assessing epigenetic factors measuring the risk of initiation of use is presented, in the next section studies analyzing epigenetic factors of progression to the development of SUD are discussed, and finally the possible implications of this approach in treatment and prevention are briefly discussed.

To find relevant articles that address the etiology of addictions from a G-E interaction perspective, a search strategy was developed in PubMed with the following search terms Addict* OR “Substance-Related Disorders” OR “behavior, addictive” AND “Gene-Environment Interaction” OR environment or “social environment” AND Causality AND Epigenetic OR Epigenomics with no time limits including articles in Spanish, English, and Portuguese. After reading the title and abstract, original articles in humans or animals that addressed the etiology of addictions according to the methodological approach of G-E interaction were included. In addition, articles from the PubMed “related articles” tool and the references of the full-text articles analyzed were included. The PubMed search strategy was also performed and adapted to the search criteria of the Ebsco, Lilacs, and SciELO databases.

RISK FACTORS FOR THE ONSET OF DRUG USE: VULNERABILITY STAGE

Identifying vulnerability risk factors for SUD has become a challenge for addiction science, which has generated significant research interest and has led to the development of numerous theories, mainly in the field of genetics¹⁸. Since the beginning of the human genome project, clinicians have been waiting to know the results and thus apply them to management protocols¹⁹.

To better understand these G-E interactions, we turn to epigenetics, which is understood as the study of stable and heritable changes in genome expression - with the particularity of being changes that do not constitute an alteration in the nucleotide sequence of the DNA molecule; that is, it is a study of the “marks” or chemical signals that modify gene activity, although without altering the structure of the gene. These “marks”, which are established during the early stages of development, are maintained in cells that divide by mitosis. The current use of the term is to indicate heritable changes in DNA structure and organization that do not involve changes in sequence and that modulate gene expression²⁰. Recently, epigenetic mechanisms have been shown to underlie drug-induced structural, synaptic and behavioral plasticity by coordinating the expression of gene networks in the brain²¹, a fact that has had application in explaining addictive behaviors.

From this epigenetic perspective, different multifactorial theories have been postulated to explain the etiology of SUD, within which have been described: 1) the additive effect of the genetic component and the environment, 2) the genetic control of sensitivity to the environment, in which genes would control the degree to which the individual is sensitive to certain aspects of the environment capable of acting as factors that increase

or decrease the expression of the disease, and 3) the influence of genotype on the susceptibility to develop a disease given by its capacity to alter the probability of exposure to predisposing environmental circumstances, thus discarding the most simplistic theories¹⁹.

Latvala et al., in a Swedish population-based study in males evaluated 3 groups with particular characteristics, in which the first group consisted of full and maternal siblings, the second consisted of full siblings raised together and separated, and the third group consisted of monozygotic and dizygotic twin brothers, concluding that genetic influence seems to be the basis for the association between low cognitive ability and the risk of psychoactive substance abuse²².

Karin et al., conducted a study in 1847 Finnish twins (943 males and 904 females) to determine the role of overlapping genetic and environmental factors in the relationship between early adolescent conduct problems and PAS use in young adulthood, finding that in males genetic influences appear to be more important in explaining the relationship between conduct disorder symptoms and substance use, while in females, shared environmental influences appear to be the most relevant²³.

For problematic use of alcohol, cannabis, and cigarettes, the role of genetic variants of the dopamine-4 receptor (DRD4) and its relationship with attachment has been investigated. Adolescents carrying a DRD4 variant called 7R+ have been found to have an increased risk of problematic cannabis and tobacco use, especially in those with insecure attachment relationships with parents²⁴. For cannabis, the interaction evidence was for anxious and avoidant attachment. This confirms what has been found in other studies that the interaction between the 7R+ allele and insecure attachment can intensify the risk of problematic cannabis, alcohol, and cigarette use^{25,26}.

PROGRESSION FROM CONSUMPTION TO THE ESTABLISHMENT OF SUD

Alcohol

The risk of alcohol use disorder (AUD) is influenced by G-E interactions, where environmental factors such as poor parental knowledge or high pairwise deviance²⁷, can affect gene expression through epigenetic mechanisms such as DNA methylation²⁸. In this sense, several studies indicate that the genes of the inactive aldehyde dehydrogenase-2 (ALDH2) and the highly active alcohol dehydrogenase 1B (ADH1B) enzymes are protective for the development of AUD²⁹. They exert their protective effect through the accumulation of acetaldehyde after alcohol consumption, generating dysplastic effects and high sensitivity to alcohol³⁰. However, the suppressive effect of ALDH2 and the high activity of ADH1B for

AUD are only partial and interact with other variables such as personality traits, psychiatric comorbidities, and environmental factors³¹. The functional variant rs1229984 of the ADH1B enzyme has been associated with AUD in several populations, but little is known about the role of the social environment as a moderator of this effect³².

Data from 1 500 European and African American adolescents from the Collaborative Study on the Genetics of Alcoholism (COGA) demonstrated that individuals with few or no best drinking friends, the ADH1B variant had a protective effect for symptoms of AUD, but in those who reported that most of their friends drank, the effect was significantly attenuated³³. These findings illustrate the interplay between ADH1B allelic variants and peer drinking on adolescent alcohol use patterns. Along the same lines, in a sample of 496 Chinese children, the polymorphism of ADH1B (rs1229984) and ALDH2 (rs671) was evaluated, whereby latent class analysis the longitudinal pattern of alcohol use was characterized, followed by multi-nominal logistic regression analysis to assess the association of these genetic variants with pubertal development and social networks³⁴. The results showed that both genes appeared to have protective effects, but such an effect was only significant in young people at the onset of puberty. These data reveal the potential moderating effect of pubertal development on the protective influence of alcohol metabolizing genes on subsequent alcohol use in children who have ever tried alcohol; also, the independent contribution of social networks early in life on alcohol involvement.

Several studies have evaluated the relationship between candidate genes for alcohol use-related problems and the moderating effect of childhood adversity³⁵⁻³⁷. For example, in a sample of 1 349 adults in Israel, it was observed that among subjects at increased risk of drinking, i.e. those who experienced childhood adversity (abuse, neglect, or parental divorce), the ADH1B-rs1229984 gene polymorphism appears to have a strong effect on the pattern of alcohol consumption and the risk of increased severity of AUD³⁸. In the same direction, the interaction between childhood adversity and the Val158Met allelic variant of the catechol-O-methyl transferase (COMT) gene is a predictor of alcohol dependence in adults³⁹. In this same context, there is evidence demonstrating a significant interaction between genetic variation in the corticotropin-releasing hormone-1 receptor gene (various haplotypes and single nucleotide polymorphisms) with traumatic experiences in adulthood as a predictor variable for the development of alcoholism⁴⁰.

Other investigators have evaluated the moderating effect of the dopamine-4 receptor (DRD4) gene polymorphism on alcohol and social bonding. In a

non-clinical sample of 720 adult social drinkers aged 21-28 years, it was observed that carriers of the 7-repeat allele of DRD4 were especially sensitive to the effects of alcohol on social bonding⁴¹. These data converge with other recent findings of G-E interactions implicating the DRD4 polymorphism in the development of AUD^{42,43}, delineating a specific pathway by which social factors may increase the risk of problematic alcohol consumption in carriers of the 7-repeat allele.

Given that some research has shown the role of the opioid receptor gene in the development of AUD^{44,45} Pfeifer et al. designed an investigation to evaluate the interaction between the mu-opioid receptor gene polymorphism (OPRM1 118G) and impulsive behavior in social drinkers. The results of the regression model showed that male social drinkers carrying the OPRM1 118G allozyme were more prone to problematic alcohol consumption and showed a greater lack of premeditation. Likewise, carriers of the G allele tended to drink more frequently due to facets of impulsivity such as urgency and lack of perseverance⁴⁶. This shows the positive correlation between genetically determined problem drinking propensity and some traits of impulsive behavior as a neurocognitive endophenotype. Similarly, significant interaction has been observed between the G allele of OPRM1 with peer deviance and parental monitoring as predictors of AUD⁴⁷.

In two large samples of adolescents in the United States and the United Kingdom, a significant G-E interaction on alcohol abuse was observed between the low activity allele of the serotonin transporter (5-HTTLPR) and exposure to high levels of family conflict, indicating that adolescents carrying the low activity allele of 5-HTTLPR are more susceptible to the effects of family conflict on alcohol abuse⁴⁸.

In the last decade, researchers have begun to see the central role of circadian cycle-related genes (clock genes) playing a central role in the acute and chronic effects of alcohol, paralleling the influence of chronic stress on the development of AUD⁴⁹. Furthermore, a reciprocal interaction between several clock genes and stress-induced alcohol abuse has been found⁴⁹⁻⁵². The allelic variant of the period-2 gene (PER2) has been associated with high stress-induced alcohol consumption in adult alcoholics, which has also been associated with a moderating effect of the rs56013859 polymorphism at position 1071 of the ATG site of PER2⁵³. Likewise, the same hPer2 gene polymorphism also moderates the impact of severe stress on alcohol abuse, as alcohol consumers carrying the G allele of the same rs56013859 polymorphism and who experienced stressful events in early adulthood (death of a loved one or relationship breakdown) drank less than homozygous carriers of the major A allele⁵⁴.

Cope et al⁵⁵ recently conducted a longitudinal community study of 218 adolescents and young adults to test the hypothesis that carriers of the short allele (s) of the serotonin transporter promoter region gene (5-HTTLPR) exhibit lower levels of responsiveness to alcohol, making them more likely to consume more alcohol, experience more alcohol problems, more heavy episodic drinking, and greater likelihood of developing an AUD. We found that the s allele was associated with high scores on an alcohol effects scale and that parental monitoring was a significant moderator of this effect. This means that one mechanism by which genetic variation in the 5-HTTLPR conveys alcohol-related risks is through the level of response to alcohol and the strength and direction of this effect is a function of the level of parental monitoring, indicating that even in the presence of genetic and physiological vulnerability, parents can influence the likelihood that their children will develop alcohol-related problem behaviors.

Given that there is a reciprocal interaction between the endocannabinoid system and chronic alcohol consumption on stress reactivity^{56,57}, it has been investigated in recent years how the social environment can moderate this relationship. In a rodent model, the pattern of alcohol use was evaluated in endocannabinoid receptor-2 (CB2)-deficient wild-type animals under different housing conditions⁵⁸. This study demonstrated that CB2 modulated alcohol consumption as lack of CB2 led to increased alcohol consumption under group housing conditions. Furthermore, CB2 knockout mice consumed more food, and their body mass index (BMI) gain was modulated by the social environment. This allows us to state that the social environment critically affects the modulatory effect of CB2 receptors, especially on alcohol intake suggesting that a therapeutic strategy targeting CB2 receptors may have a beneficial effect on pathological alcohol consumption, especially in situations of social stress and discomfort.

Nicotine

Twin smoking studies⁵⁹ report an increased genetic influence on adolescent smoking in the presence of low parental monitoring. In addition, a study of nicotine dependence in adults aged 25-44 years reported a significant interaction between parental monitoring of adolescents and a variant of the α -5 subunit of the nicotinic acetylcholine receptor (CHRNA5, rs16969968); genetic risk was reduced in participants with high levels of parental monitoring⁶⁰. In addition, the genetic risk of smoking was reduced in individuals who lived in neighborhoods with a high level of social cohesion⁶¹. In a study conducted by Olsson et al., an attempt was made to evaluate the combined effect of a dopamine receptor

4 (7R+) allelic variable and insecure attachment on the development of smoking-related problems in early adulthood. It was found that the interaction between the 7R+ allele and insecure attachment could intensify the risk of problematic tobacco use²⁴. Similarly, in a sample of Hungarian smokers, a combined effect of the α 4 β 2 nicotinic acetylcholine receptor polymorphism (α 4 β 2) and the relationship with maternal parenting style on the development of nicotine dependence was found⁶².

Cannabis

Given the interactions between the endocannabinoid system (e-CBS) and the stress system^{63,64} and the actions between childhood stress and involvement in cannabis use,⁶⁵⁻⁶⁷ recent research has addressed childhood adversity in the context of e-CB genetic variation in the development of cannabis addiction. Using the Trauma and Comorbidity Study database (N = 1,558), Carey et al assessed whether genetic variation in 6 endocannabinoid system (e-CB) genes and childhood sexual abuse were predictors of cannabis dependence symptoms⁶⁸. Significant interactions were observed between variants of the monoacylglycerol lipase-MAGL (MAGL) gene (rs604300) with early adversity and cannabis dependence, i.e., carriers of the major G allele were at increased risk for cannabis dependence as exposure to early adversity increased. These results suggest that rs604300 may be related to epigenetic modulation of MAGL enzyme gene expression, which is consistent with data from rodent models implicating the e-CB system in the etiology of stress adaptation related to cannabis dependence⁶⁹⁻⁷¹.

Cocaine

In the last decade, interest has been generated in studying G-E and gene-gene interactions⁷² in psychoactive substance addiction through the association between childhood neglect and polymorphism of the mineralocorticoid (NR3C2) and glucocorticoid (NR3C1) genes⁷³⁻⁷⁵. In this sense, Rovaris et al evaluated 139 cocaine-addicted women in the withdrawal period, finding a significant interaction between the rs5522 allele of NR3C2 and lack of infant physical contact, which altered the risk of cocaine addiction (OR = 4.0, p = 0.001). In addition, the NR3C2-NR3C1 gene interaction (p = 0.002) modulated the severity of cocaine withdrawal symptoms⁷⁶. This G-E interaction is consistent with human epidemiological and experimental findings demonstrating a strong relationship between early life stress and hypothalamic-pituitary-adrenal (HPA) axis dysregulation⁷⁷ in cocaine and tobacco addiction⁷⁵.

As we can see, G-G and G-E interactions may play a critical role in cocaine addiction, but few studies have

demonstrated the impact of candidate genes on complex traits or how these interactions may be modulated by external conditions⁷⁸.

In animal studies, genetic variation in catecholamine receptors and environmental cues converge to regulate decision-making⁷⁹ which is a key trait in addictive behavior (gene-gene-environment interaction)⁸⁰. In this context Sullivan et al evaluated whether gene-gene-drug (environment) interaction affected the risk of cocaine-induced death, using genetic statistical methods⁸¹. The design was case-control using postmortem samples of prefrontal cortex and ventral putamen in cocaine abusers who died from intoxication compared with controls who died from other causes. We found that the DRD4 rs2283265 polymorphism encoding the D2 receptor conferred a risk of cocaine overdose/death (OR~3) in cases and controls. However, the risk of cocaine-related death attributable to the minor allele was significantly increased OR=7.5 (P=0.0008) in homozygous carriers of the major rs3836790 allele of the dopamine transporter (DAT) vs the minor allele (OR=1.1, P=0.84). The DAT rs3836790 and dopamine receptor-2 (DRD2) rs2283265 polymorphisms also interacted with dopamine transporter protein activity in the ventral putamen of cocaine abusers. These results demonstrate a complex gene-gene-drug interaction that affects the risk of fatal cocaine intoxication. It also provides data on genetic interactions that may help close the gap of a missing heritability percentage that exists in addictions⁸².

Similarly, recent evidence suggests that genetic variations impacting 5-HT activity and 5-HT transporter (5-HTT) mRNA expression are associated with working memory performance in cocaine users. In cocaine users, several 5-HTTLPR alleles increased the risk for working memory (WM) impairment, whereas in controls these polymorphisms were associated with improved WM performance. Similarly, high 5-HTT mRNA levels were associated with worse WM performance in cocaine users, but with increased performance in controls⁸³. These G-E interactions suggest that the serotonergic system plays an important role in the development of cognitive deficits in chronic cocaine users, so pharmacological strategies targeting serotonergic transmission could be promising for the treatment of cognitive deficits in cocaine dependence.

Amphetamines

The netrin-1 receptor encoded by the netrin-1 receptor gene (DCC), is upregulated upon repeated administration of amphetamine selectively in the ventral tegmental area (VTA) of adult rats and wild-type mice^{84,85}. Furthermore, adult DCC heterozygotes do

not show these amphetamine-induced increases in DCC expression in the VTA and do not develop sensitization to amphetamine⁸⁴⁻⁸⁶. Few studies investigate the effect of environmental factors on this phenomenon. Consequently, Yetnikoff et al., evaluated the effects of netrin-1 receptor signaling on the mesocorticolimbic dopaminergic system and its changes throughout development⁸⁷. Repeated amphetamine administration produces down-regulation of DCC expression selectively in the VTA of juvenile rodents. Furthermore, the behavioral phenotype of DCC heterozygous adult mice was not present before puberty and is abolished by amphetamine administration during the juvenile period. Surprisingly, DCC heterozygous adults pretreated with amphetamine as juveniles no longer show reduced expression of DCC in the VTA compared to wild-type controls. These results indicate that netrin-1 receptor signaling may be a key factor in determining individual differences in vulnerability to the behavioral sensitization effects of amphetamine at different ages. Furthermore, they suggest that the juvenile period represents a window of vulnerability during which exposure to stimulant drugs can reverse the behavioral phenotype of heterozygous adult mice⁸⁸.

There is evidence that rats exposed to enriched environments alter psychostimulant-induced locomotor activity^{89,90}. Exposure to novelty and psychostimulants induces the expression of c-fos (a cellular proto-oncogene belonging to the family of rapidly expressed gene transcription factors.) in neurons of the mesolimbic dopaminergic pathway; therefore, in recent years, changes in c-fos expression in the mesolimbic DA pathway have been investigated in rats bred in different environments due to neurobiological changes determined by breeding conditions and which influence drug intake behavior^{91,92}.

Gill et al⁹³, performed experiments on rats reared in an enriched environment (EC), isolation (IC), social (SC) conditions for 30 days after amphetamine administration followed by c-fos labeling in various brain regions. It was observed that rats reared in IC demonstrated higher c-fos expression than those exposed to EC in the nucleus accumbens (NAcc) when treated with amphetamine. Additionally, amphetamine-treated IC rats displayed higher c-fos expression in NAcc compared to IC rats receiving saline (SSN), whereas SSN and EC rats showed higher c-fos expression in the prelimbic cortex compared to amphetamine-treated EC rats. This evidence a regional specificity in psychostimulant-induced c-fos expression in the prelimbic and NAcc pathway, which is modified by differential rearing, influencing c-fos activation after psychostimulant exposure, findings that have been reproduced in other experiments with glutamate receptor subunit expression⁹⁴.

Opioids

Several studies have suggested that maternal deprivation predisposes male rats to anxiety with increased opioid consumption⁹⁵⁻⁹⁷, however, there are few studies on epigenetic mechanisms that explain this phenomenon⁹⁸. Therefore, Tesone-Coelho et al., evaluated the expression of methylated binding protein (MeCP2- methyl-CpG-binding protein), histone deacetylases HDAC2/HDAC3, as well as the acetylation status of histones H3 and H4 in mesolimbic structures of maternally deprived adult rats. These experiments found a long-lasting increase in MeCP2 expression in the striatum of deprived rats. They further found increased HDAC2 expression and increased nuclear HDAC activity in the NAcc of deprived rats that were associated with decreased histone H3 and H4⁹⁹ acetylation. Furthermore, treatment for 3 weeks with the HDAC inhibitor sodium valproate suppressed HDAC activation along with decreased levels of histone H4 acetylation which was accompanied by normalization of oral morphine consumption¹⁰⁰. These findings indicate that epigenetic mechanisms induced by the adverse environment leave a memory mark that triggers increased vulnerability to opioid consumption during adulthood. It further suggests that sodium valproate may decrease that vulnerability to opioid intake, particularly in subgroups of individuals exposed to adverse postnatal environments.

Growing evidence indicates that microglia and astrocytes can affect the reinforcing properties of drugs, including morphine^{101,102}. Accordingly, Schwarz et al., in a rodent model have shown that glia within the rat NAcc responds to morphine with increased cytokine expression, which predicts the reinstatement of morphine preference followed by a priming dose; this glial response is influenced by early life experience¹⁰³. A neonatal care paradigm that increases the quantity and quality of maternal care significantly increased basal expression of the anti-inflammatory cytokine IL-10 in the NAcc, which attenuates morphine-induced glial activation preventing reinstatement of morphine preference in adulthood. This inverse correlation of IL-10 expression in the NAcc and the reappearance of morphine preference suggests a protective effect of this cytokine against morphine-induced glial reactivity and the reinstatement of morphine preference induced by the same drug. Finally, it is striking that neonatal care programs IL-10 expression in the NAcc in early development, and this is maintained in adulthood through decreased IL-10 gene methylation especially in microglia.

THERAPEUTIC IMPLICATIONS

The identification of specific environments that modify the expression of genetic risk predispositions

may create areas of emphasis for the prevention and treatment of SUD¹⁰⁴. Focusing on G-E interactions will not only provide insights into the underlying biological mechanisms but will also allow the characterization of subgroups (based on environmental factors) at high risk for addictive behaviors that can be targeted for specific interventions². For example, interaction has been evidenced between polymorphism of the cholinergic nicotinic receptor alpha-5 subunit (CHRNA5) gene and the success of nicotine replacement therapy. Individuals with higher risk genotypes were more likely to benefit from treatment¹⁰⁵.

A therapeutic application of the findings in epigenetic research is the fact that the protective effect of neonatal care in rats on addictive behavior can be mimicked by pharmacological modulation of glia in adulthood with the drug Ibudilast, which increases IL-10 expression, inhibits morphine-induced glial activation in the NAcc and prevents the reinstatement of conditioned place preference to morphine¹⁰³⁻¹⁰⁶.

The contribution of genetic studies has revealed the critical role of epigenetic modifiers in maintaining brain homeostasis under pathological conditions, so that histone acetylation may provide a benefit for the treatment of SUD¹⁰⁷. Indeed, the evidence supporting the role of HDACs modifying drugs is compelling¹⁵. For example, HDAC5 is involved in chromatin changes and gene alterations induced by drugs and stressful stimuli¹⁰⁸; although the impact of HDAC5 on the reinforcing effects of cocaine are not entirely clear, its overexpression has been shown to amputate conditional preference of place to cocaine and the effects on cocaine locomotor activity.

Epigenetic research has also succeeded in raising interest in HDAC inhibitors (1) such as Trichostatin A, valproic acid, sodium butyrate¹⁰⁹, which may help to strengthen the scientific rationale for the use of these drugs in SUD. A more recent therapeutic approach is the use of small interfering RNA coupled with gold nanoparticles to silence the DARP-32 gene (Dopamine-AMP-cyclic AMP-regulated protein phosphatase inhibitor) in dopaminergic cells¹¹⁰, known to be one of the key regulators of histone acetylation.

Despite these advances, without collaborative work between researchers working in addiction genetics and those working in prevention and treatment, it is difficult to translate research results into practice^{14,111}. Perhaps the most promising strategy is deep cooperation between basic applied science researchers and clinicians through joint work, the construction of knowledge networks, and scientific associations^{14,112}. Finally, any field of knowledge is more likely to advance if its actors are permanently reevaluating the answers to their questions and their theoretical positions¹¹³.

CONCLUSIONS

Epigenetics is understood as the sum of a whole (environment, agent, and susceptibility of the organism) explains broadly the vulnerability, onset, progression, and establishment of SUD.

There is no doubt that altered histone acetylation status is a major contributor to the transition to SUD. However, research in the field of drug dependence needs to focus more on specific HDAC modulators that target the drug memory footprint and how this can translate into effective medications to prevent drug relapse.

Current treatment strategies for substance use disorders should not only focus on the individual and cessation of substance use but also on the developmental and social

processes that may perpetuate addiction. Therefore, we believe that combining psychosocial interventions with gene therapy involving pharmacological manipulations of histones may contribute to designing better therapies and perhaps lead to more successful management of drug dependencies.

Despite all this, it is clear that more research is needed to consolidate the field of interactions between genetic and environmental factors in addictions¹¹⁴.

DECLARATION OF CONFLICTS OF INTERESTS

The authors declare they have no conflicts of interests.

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