Epigenetic regulation in drug addiction

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Abstract

The interaction between environmental signals and genes has now taken on a clear molecular form as demonstrated by stable changes in chromatin structure. These changes occur through activation or repression of specific gene programmes by a combination of chromatin remodelling, activation and enzymatic modification of DNA and histones as well as nucleosomal subunit exchange. Recent research investigating the molecular mechanisms controlling drug-induced transcriptional, behavioural and synaptic activity has shown a direct role for chromatin remodelling – termed as epigenetic regulation – of neuronal gene programmes and subsequent addictive behaviour arising from it. Recent data suggest that repeated exposure to certain drugs promotes changes in levels of histone acetylation, phosphorylation and methylation, together with alterations in DNA methylation levels in the neurons of the brain reward centre, localised in the Nucleus Accumbens (NAc) region of the limbic system. The combination of acetylating, phosphorylating and methylating H3 and H4 histone tails alter chromatin compaction thereby promoting altered levels of cellular gene expression. Histone modifications, which weaken histone interaction with DNA or that promote recruitment of transcriptional activating complexes, correlate with permissive gene expression. Histone deacetylation, (which strengthen histone: DNA contacts), or histone methylation, (which recruits repressive complexes to chromatin), promote a state of transcriptional repression. Using animal models, acute cocaine treatment increases H4 acetylation at acutely regulated gene promoters, whereas H3 acetylation appears to predominate at chronically induced promoters. Chronic cocaine and alcohol treatment activate and repress many genes such as *FosB*, *Cdk5*, and *Bdnf*, where their dysregulation, at the chromatin level, contribute to the development and maintenance of addiction. Following drug exposure, it is still unknown, howver, how long these changes in chromatin structure persist in affecting neuronal function, but some do so for life.

Keywords

chromatin, histone, acetylation, phosphorylation, methylation, drug addiction

ORIGINS OF EPIGENETICS

The term 'epigenetics' is derived from the Greek Word 'epi' meaning 'above', 'over' or 'in addition to' and applies to regulating gene activation by extra-genetic factors that exclude changes in nucleotide DNA sequence of the genome, for example, such as those caused by gene mutation. The processes of gene activation, repression of already active ones, inhibiting translation and transcription, is thus not only DNA-related, but can also come from the extracellular environment of given organism. The concept of epigenetics was first introduced in 1942 by Conrad Waddington, [1], and defined as the study of gene expression and phenotypic changes beyond the genome, together with their heritability, including those also invoked by the environment. This came about from studies on cellular differentiation during embryonic development [1] where various structures with different forms and functions were found to originate from common pluripotent mother cells with identical genomes. Reasons were sought for why such differing cell characteristics could be manifested in the phenotype leading to the differentiation in cellular function of tissues, organs, etc., for example, comparing cardiac muscle with nervous tissue (i.e. neurones).

Similar questions were also posed by Waddington concerning monozygotic twins who possess identical genomes, but who can demonstrate marked phenotypic variation in many traits. It should be pointed out, however, that at this time, DNA structure was as yet unknown as was the genetic code, nor obviously were the molecular mechanisms of heritability, i.e. transcription, translation or protein synthesis; molecular biology being then in its infancy. Despite these drawbacks, Waddington should be further congratulated on introducing the important concept of an 'epigenetic landscape' which picturised epigenetic regulation of the genome as applied to the husbandry of plants, shrubs and trees, i.e. phenotypic variation can arise from epigenetics based on the genotype [1].

In recent years, epigenetics has witnessed intensive study and development resulting in this field now becoming recognised as vitally important in determining heritable

changes in gene expression achieved without changes to the underlying DNA sequence. An analogy has been made to a 'puppet theatre' where genes are the puppets pulled by the strings of epigenetic machinery, mediated by activated histone proteins that decide which genes are active and which are silenced.

THE PREDOMINANCE OF DNA AND THE NEW ROLE OF THE ENVIRONMENT

Epigenetic studies have since undermined the belief of the genetic determinism of DNA, and now show that genetic information encompassed within DNA is not constant but is also influenced by physiological and pathological factors arising from the environment. These acts, during embryonic and post-natal development and also in adulthood, amongst others, may include the quality and type of nutrition, stress, emotional state, upbringing, education, and even how information is stored in the memory [2, 3, 4, 5]. The notion that DNA is the sole regulator and controller of biological function and hereditability has been superseded by the acknowledgement that the environment can play similar roles in regulation mediated by histones on DNA and RNA, and thus on the critical target step of protein synthesis. Most significantly, epigenetic modifications in histones/chromatin pass between generations without alteration to the DNA sequence. This development, however, has not been fully explained in terms of transgenerational mechanisms of hereditability acquired from parental traits that are passed on to the offspring. Nevertheless, advanced analytical methods/approaches used nowadays have clearly demonstrated this as a likely biological mechanism [4, 6].

The 'epigenetic landscape' mentioned above has been the subject of many recent studies at subcellular and molecular levels demonstrating that the environment can affect lasting changes in chromatin structure, thereby influencing regulatory transcription proteins which, in turn, can switch-off or switch-on certain gene programmes [7]. Epigenetic changes actually occur through chromatin remodelling, enzymatic modification of histone proteins or those in the nucleosome. These alterations in chromatin structure are linked to DNA methylation, modulation of targeted promoters by small non-coding RNAs, histone variants containing amino acid substitutions, or post-translationally modified histones that change the shape of chromatin [8]. When studying addiction, epigenetic regulation through induction/activation is mostly through chromatin remodelling and the post-translational changes to histones. The former, together with long-lasting/permanent changes in transcriptional mechanisms and neuronal plasticity, has been observed in addicts, which has generated new studies in order to find improved treatments and therapies, as well as preventing the addiction in the first place.

THE EPIGENETIC CODE

Nuclear DNA is coiled in a precise manner around spherical histone proteins in a fashion somewhat analogous to thread being wrapped around a bobbin and constitute the nucleosome core particle. This DNA doubly-coiled segment consists of 147 base pairs, and the histone is an octomeric protein consisting of 2 copies of 4 core histones, termed H2A, H2B, H3, and H4 [9]. There are 2 ways the nucleosomes can be stacked in chromatin: one keeps the structure compact, i.e. heterochromatin, while the other is looser and named euchromatin. The latter ensures that the DNA gene segments are more active and better able to initiate transcription information from DNA to RNA. The former, however, prevents the access of transcription factors to DNA, thus making the gene inactive, i.e. suppressed. These 2 forms of chromatin are, for example, linked to neuronal function in the brain's reward system where protein synthesis and neurotransmitter release is initiated, and whole networks of neurones are stimulated in a durable manner [10]. The degree of looseness in which DNA is coiled depends on the type and amount of substitution in the histone proteins by enzymatic methylation, acetylation and phosphorylation, as well as many other N-terminal modifications on the histone tails. In turn, the degree to which histones are saturated by these modifications determines whether genes become activated or suppressed; thus, most of the changes in chromatin packing thereby affect a given synthesis of protein through these 2 ways. These many modifications to the amino acid residues of histone therefore leave a mark, and indeed the end products are termed gene activator/suppressor markers and have lately been called epigenetic markers/marker factors, as they arise outside the DNA. As alluded to previously, such histone modifications are achieved by specific enzyme action (e.g. acetyltransferase, methyltransferase, phosphorylase); however, they are reversible by the corresponding deacetylase, demethylase and dephosphorylases which can also act whenever it becomes necessary to revert back to the original functional state of the gene before the epigenetic modification and change in packing had occurred [11].

Epigenetic chromatin modifications may, on one hand, be short-term, lasting minutes, or those that endure for months and even years in examples of chronic abuse of addictive substances in humans or animals. In addicts, the actual mechanisms that govern how long these epigenetic changes last, however, are little understood, some lasting for years or even a lifetime. The persistence of such changes will influence how effectively addicts are treated, given the high tendency to relapse even after many years of abstinence [12].

Thus, the programming of epigenetic modification of chromatin involves dynamic change where the action of the afore-mentioned factors, together with many others coming into play at different stages, in the end are summed-up to ultimately result in gene activation or suppression. In conclusion, the process is described as the epigenetic code of multiple dynamic chromatin modification which systematically regulates gene transcription. A full description, however, lies outside the scope of this review and only those examples which are pertinent to drug addiction in human or animal models are considered further. This epigenetic/histone code terminology is frequently used to describe the afore-mentioned chromatin modification because, like the genetic code, the outcome is protein synthesis which govern changes in neuronal function, especially in the reward system [13]. In contrast to the genetic code, epigenetic coding is characterised by dynamic change linked to different levels of sensitivity to environmental change and its duration which, taken as a whole, therefore enables a given organism to adapt its behaviour accordingly with a very high degree of control [14].

Annals of Agricultural and Environmental Medicine 2012, Vol 19, No 3
493
Przemysław Biliński, Andrzej Wojtyła, Lucyna Kapka-Skrzypczak, Roman Chwedorowicz, Małgorzata Cyranka, Tadeusz Studziński. Epigenetic regulation in drug addiction

EPIGENETIC REGULATION AND ADDICTION

In recent years, epigenetics mechanisms have become significantly implicated in disease induction, including the aetiology of cancer, diabetes, Alzheimer's, schizophrenia, autism and depression. It was also hardly surprising to find that changes in histones and chromatin occur when drugs/addictive substances are taken. It appears that modified histones induce typical drug-related neurobiological reaction behaviour, which can also readily arise when such substances are taken after long abstinence [15]. Among these epigenetic considerations with addiction there also lies an inherited genetic predisposition in people, which accounts for 50% of those susceptible to addiction and who become established addicts [16, 17, 18, 19]. Despite the many wide-ranging genetic studies that have determined which of the many genes are linked to high addiction risk, it is the influence of inducing potentiating epigenetic factors, such as the environment, habits, cultural and social, that make up the remaining 50% susceptible to addiction through this epigenetic regulation. For this reason, of necessity, addiction studies have been directed at understanding the underlying epigenetic mechanisms, and holds promise in explaining many complex phenomena concerning the structure and function of neurones, especially in chromatin modelling and their influence on gene activation.

In order to achieve a more complete understanding of addiction, it would therefore appear necessary to include epigenetics in any future studies as this psychiatric disorder has such a varied etiology, ranging from inherited genetic causes of predisposition to environmental (epigenetic) factors. This includes looking at transient and long-lasting changes in gene activation/repression that determine the individual's tolerance, as well as behavioural sensitivities to addictive substances. Being addicted to drugs is currently defined as losing control over their consumption, actively seeking them out, the compulsion to take them despite their clearly obvious harmful effects on health, and the development of uncharacteristic disturbed behaviour patterns becoming similar to pathological behaviour. The duration and stability of such symptoms in addicted persons most likely indicates that epigenetic changes have occurred in neuronal chromatin structures of the CNS and, in effect, have led to them being ever present, even when the first dose of drugs has been taken and experienced [20].

It has also been seen that epigenetic changes mediated by drugs/addictive substances have shown special resistance to any treatment of addicts by conventional means/therapies where individuals also retain being vulnerable to relapse, thus overall deepening the addiction [21]. Altered gene expression has been observed in neurones of the brain's reward, motivation and pleasure centre (i.e. brain reward regions), when addictive drugs are taken. These changes are maintained for many months after abstinence from cocaine, opioids, alcohol, and other similar substances. The underlying responsible mechanisms, however, are still unknown, despite intensive molecular biology investigation. It has only more recently been found that long-lasting epigenetic modifications in this brain area are in fact significant. The first studies performed on animals demonstrated epigenetic changes in 100 genes from neurones of the brain's accumbens nucleus, i.e. the above-mentioned brain reward regions. However, before the epigenetic link to gene activation and function had

been established, during acute/chronic exposure to addictive substances, the mechanism activating dopaminergic transmission had been elucidated in the brain's reward centre which is localised in two areas of the anatomically defined limbic region, i.e. the Ventral tegmental field (VTA) and Nucleus Accumbens [22, 23].

When addictive drugs are taken, the neurones from the latter receive a huge dopamine input, eliciting a state of blissful euphoria where the physiological dopamine concentrations are exceeded many times over, leading to an increased sensitivity to drugs and their addiction. Although the role of dopaminergic transmission in the reward centre is now known, together with that of other neurotransmitters (noradrenaline, serotonin and glutamine), as well the intracellular pathways that addictive drugs take to exert their effect, the mechanisms of gene expression/repression during an addiction are not. Adoption of the recent epigenetic approach has now enabled discovery of the role that is played by enzymes, chromatin/histone remodelling and transcription factors which are responsible for long-lasting changes to gene expression when addictive drugs are taken [15, 24, 25].

EPIGENETIC ADAPTATION OF NEURONES IN THE ACCUMBENS NUCLEUS CAUSED BY TAKING COCAINE

The basic aim of epigenetic studies on addiction is to determine which genes are involved, and their mechanisms of activation and stability, ranging between when drugs are taken occasionally to chronically. Four basic objectives can be discerned:
- Identifying those genes the expression of which is influenced by drugs of abuse
- Determining neuronal *in vivo* transcription mechanisms engaged in signal neurotransmission
- Investigating the underlying mechanisms that induce long-term and stable addictive behaviour.
- Developing more effective drugs and treatments for drug addiction.

Most studies on neuronal mechanisms of drug action have been conducted with cocaine using animal models; being closely similar if not identical to the effects of alcohol and other addictive substances. In particular, this has included stimulatory signal transmission between and within neurones, together with gene expression during chronic exposure to cocaine and other drugs; some differences in effect were noted, however, with acute exposures. Key drug effects during this neurotransmission cascade were localised intracellularly to the Accumbens nucleus of the ventral striatum and other limbic areas, and consisted of activating or suppressing transcription factors and regulatory proteins of chromatin. The outcome then being expression/suppression of certain genes responsible for affecting signal transmission at synapses, synaptic receptors and intracellular levels, together with exerting an influence on the neuronal cytoskeleton and dendtritic development for making new neuronal connections. Both acute or chronic intake of cocaine causes increased activation of many genes, but after a single dose they return to previous levels. Long-term cocaine abuse also results in some genes being activated to a greater extent; however, some remain highly active and do not return to starting levels while others fall

494

Annals of Agricultural and Environmental Medicine 2012, Vol 19, No 3

Przemysław Biliński, Andrzej Wojtyła, Lucyna Kapka-Skrzypczak, Roman Chwedorowicz, Małgorzata Cyranka, Tadeusz Studziński. Epigenetic regulation in drug addiction

below this level. This differential effect on gene activation and expression is manifested as either a high sensitivity or complete insensitivity to repeated drug doses which, in the latter, arises from gene desensitisation. Such changes in the reward centre thus also lead to a craving for taking higher drug doses to recapture the same state of euphoria obtained when the drug was originally first taken in much smaller amounts and single doses. These effects can be explained by the levels that H3 and H4 histones become acetylated, phosphorylated and methylated, [15, 25, 26]. When the first ever cocaine dose is taken, i.e. an acute experimental dose, then chromatin becomes more densely packed, thereby decreasing the access to transcription factors and thus reducing gene activation. The effect is mediated by hyper-activation of histone methyltransferase (HMT) and deacetylase (HDAC), ensuring that methylation predominates, resulting in gene repression [24].

Chronic treatment with cocaine, however, shows the reverse where acetylation predominates at the expense of methylation due to the respective enzymes being activated and inhibited, coupled with increasing levels of ΔFosB and CREB, (Cyclic AMP Response Element Biding Protein), transcription factors. The latter two, together with RNA and Polymerase II, activate the expression of genes responsible for inducing neuronal plasticity in the Accumbens nucleus [10, 27, 28]. Chronic cocaine treatment of laboratory animals showed hyper-acetylation on histone H3, producing a stable activation level of those genes affected in the NAc, e.g. cdk5 (Cyclin-dependent kinase), bdnf (Brain-derived neurotrophic factor) or npy (Neuropeptide Y) [24]. A similar increase in the expression of these genes, concomitant with histone hyper-acetylation, has been seen in mouse Prefrontal cortical neurones following the withholding of cocaine after chronic cocaine treatment. Furthermore, acute cocaine treatment showed H4 acetylation to predominate, whereas after chronic treatment this occurred in H3. In addition, the afore-mentioned transcription factors (ΔFosB and CREB) were induced by cocaine which play a key role in regulating those genes which adapt to chronic cocaine treatment, as well as other psychostimulants [10].

Methylation of histones is a vital consideration in the cocaine-induced remodelling of chromatin. Chronic cocaine treatment reduces the dimethylation of lysine 9 on histone H3, (H3K9me2) in the Accumbens nucleus (through suppressing the $G9a$ gene coding for histone-dimethyltransferase), which modifies the expression of many other genes. Cocaine also induces high ΔFosB levels which inhibits the histone-dimethyltransferase, thus, in addition reducing the H3 dimethylation. The combined effect is an increased sensitivity to further doses of cocaine where behavioural responses are intensified as measured by increased motor activity. Also seen is a huge increase of neuronal dendrites in the NAc forming new glutaminergic synaptic connections thereby stimulating the limbic system that includes the reward centre. This dendritic arborisation caused by increasing ΔFosB levels is stable and long lasting due to a lack of 2 domains and phosphorylation of serine residues. The effect of ΔFosB on structural plasticity arise from wide ranging action on many genes whose expression stimulate kinases, synaptotagmins, actin-like protein, microtubule structure regulators and Cyclin-dependent kinase 5 (CDK5). For these reasons, ΔFosB is considered a primary and causative transcription factor in creating new neural connections in the reward centre,

prefrontal cortex, and other regions of the limbic system. This is reflected in the increased, stable and long-lasting level of sensitivity to cocaine and other drugs, and tendency to relapse even after long periods of abstinence. These newly-constructed networks function very efficiently via new pathways as soon as drugs of abuse are further taken [29].

An important part of the cocaine mediated ΔFosB effect is on the above-mentioned $CDK5$ gene, the action of which is associated with additional recruitment and activation of regulatory proteins and transcription factors that can either activate or suppress genes. In this way, the induction of $CDK5$ gene expression occurs together with suppression of the $G9A$ gene coding for dimethyltransferase acting on the histone H3. A feedback mechanism can be observed in the regulation of these 2 crucial factors that determine the adaptive epigenetic response to cocaine. This depends on ΔFosB inhibiting $G9a$ gene expression, i.e. H3K9me2 synthesis which in turn inhibits transcription factors for ΔFosB. For this reason, the observed hyper-expression of $G9a$, which ensures high levels of the dimethylated form of histone H3, eliminates the neuronal structural and plasticity effects caused by cocaine by means of this feedback which blocks ΔFosB transcription [25].

Taking cocaine therefore elicits epigenetic transmission of a signal in the reward centre neurones, involving histone proteins, transcription factors, and gene activation, together with the lastly-described feedback. These targets provide an invaluable opportunity for designing new drugs which could prove more efficacious in addiction therapy, as well as in making prevention more effective.

THE DEVELOPMENTAL PROGRAMMING OF ADDICTION (BARKER'S HYPOTHESIS)

Extensive research demonstrates that pregnant women smoking tobacco during foetal intrauterine development influences how often their offspring will smoke, and also increases the vulnerability to smoking addiction in later life [30, 31]. Nicotine, as well as directly acting on neuronal development (mainly via acetylcholine receptors), also changes gene expression, thereby affecting cellular replication and differentiation within the brain [32]. In later years, these effects influence the vulnerability to tobacco addiction after birth [33, 34, 35]. Similar findings are also observed with alcohol [36], which freely passes through the placental barrier, where enzymatic degradation in the foetus is minimal; thus, foetal tolerance to alcohol is low [37]. As a result, drastic exposures to high alcohol concentrations may cause a sudden stillbirth or spontaneous abortion. Alcohol exposures during foetal intrauterine development can also lead to the Foetal Alcohol Syndrome (FAS), Foetal Alcohol Spectrum Disorders (FASD), and Alcohol-Related Neurodevelopmental Disabilities (ARND) [38], together with the offspring becoming more vulnerable to frequent alcohol drinking and addiction in later life [39]. Furthermore, if the mother has an alcohol addiction then the offspring's phenotype will likewise become susceptible after birth, according to Barker's hypothesis on 'Foetal Origins of Adult Health and Disease' [40, 41, 42, 43, 44].

The hypothesis also defines the period of foetal intrauterine development as 'Developmental Plasticity' where environmental signals shape the phenotype [45].

Annals of Agricultural and Environmental Medicine 2012, Vol 19, No 3

495

Przemysław Biliński, Andrzej Wojtyła, Lucyna Kapka-Skrzypczak, Roman Chwedorowicz, Małgorzata Cyranka, Tadeusz Studziński. Epigenetic regulation in drug addiction

The process depends on gene expression thus possessing an epigenetic basis. In addition to alcohol, other studies have shown that this also applies to psychoactive substances, drugs and tobacco [46], and to the age at which experimenting and abuse of these substances start during teenage [47]. With cocaine abuse, two pathological mechanisms can be discerned in foetal intrauterine development: neurochemical and vasoconstrictive effects. In addition, a third has now been recognised concerning the effect on foetal programming. This depends on epigenetic changes due to cocaine intake from the intrauterine environment during prenatal phenotypic development [48] where cocaine acts as a stressor; changing gene expression in those genes affecting the activity of the hypothalamic-pituitary-adrenal axis. As a result, cortisol and catecholamine levels are elevated. In turn, this causes changes in infancy and childhood behaviour that becomes dysregulated, emotionally uncontrolled with a greater tendency to substance abuse in later life. These recent observations, indeed now confirm previous findings [49, 50].

SUMMARY

This paper shows that the epigenetic regulation of gene expression has now become a matter of great importance in understanding the mechanisms which are involved in drug addiction development. As mentioned previously, epigenetic mechanisms have been found to occur in response to illicit drug use or as underlying factors in chronic substance abuse and relapse. The identification of cocaine-induced alterations in histone acetylation, phosphorylation and methylation in the NAc and other brain areas suggests that such modifications might be involved in regulating also the behavioral responses to drugs of abuse. The studies by Kumar *et al.* demonstrated that the pharmacological and genetic manipulation of certain HDACs in the NAc alters levels of histone acetylation *in vivo,* and profoundly affects behavioural sensitivity to cocaine. Such regulation provides a new layer of complexity at the molecular level, through which cocaine produces neural and behavioural plasticity, and reveals mechanisms for the treatment of cocaine addiction that involve interfering with this plasticity [24].

Ultimately, elucidating the exact mechanisms of epigenetic regulation of pathogenesis of drug addiction has important implications for therapy because of the novel therapeutics that could target such mechanisms to block or even reverse the transition from recreational drug use to a chronically addicted state [15]. Even more important is the chance to reveal novel drug targets for the development of improved pharmaceutical interventions in the case of reversing developmental programming of addiction in offspring of mothers, either addicted to drugs, alcohol, tobacco [35], or having different kinds of disorders [6], and thereby making early prevention more effective.

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496

Annals of Agricultural and Environmental Medicine 2012, Vol 19, No 3

Przemysław Biliński, Andrzej Wojtyła, Lucyna Kapka-Skrzypczak, Roman Chwedorowicz, Małgorzata Cyranka, Tadeusz Studziński. Epigenetic regulation in drug addiction

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