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Epigenetic side-effects of common pharmaceuticals: A potential new field in medicine and pharmacology

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SUMMARY

The term "Epigenetics" refers to DNA and chromatin modifications that persist from one cell division to the next, despite a lack of change in the underlying DNA sequence. The "epigenome" refers to the overall epigenetic state of a cell, and serves as an interface between the environment and the genome. The epigenome is dynamic and responsive to environmental signals not only during development, but also throughout life; and it is becoming increasingly apparent that chemicals can cause changes in gene expression that persist long after exposure has ceased. Here we present the hypothesis that commonly-used pharmaceutical drugs can cause such persistent epigenetic changes. Drugs may alter epigenetic homeostasis by direct or indirect mechanisms. Direct effects may be caused by drugs which affect chromatin architecture or DNA methylation. For example the antihypertensive hydralazine inhibits DNA methylation. An example of an indirectly acting drug is isotretinoin, which has transcription factor activity. A two-tier mechanism is postulated for indirect effects in which acute exposure to a drug influences signaling pathways that may lead to an alteration of transcription factor activity at gene promoters. This stimulation results in the altered expression of receptors, signaling molecules, and other proteins necessary to alter genetic regulatory circuits. With more chronic exposure, cells adapt by an unknown hypothetical process that results in more permanent modifications to DNA methylation and chromatin structure, leading to enduring alteration of a given epigenetic network. Therefore, any epigenetic side-effect caused by a drug may persist after the drug is discontinued. It is further proposed that some iatrogenic diseases such as tardive dyskinesia and drug-induced SLE are epigenetic in nature. If this hypothesis is correct the consequences for modern medicine are profound, since it would imply that our current understanding of pharmacology is an oversimplification. We propose that epigenetic side-effects of pharmaceuticals may be involved in the etiology of heart disease, cancer, neurological and cognitive disorders, obesity, diabetes, infertility, and sexual dysfunction. It is suggested that a systems biology approach employing microarray analyses of gene expression and methylation patterns can lead to a better understanding of long-term side-effects of drugs, and that in the future, epigenetic assays should be incorporated into the safety assessment of all pharmaceutical drugs. This new approach to pharmacology has been termed "phamacoepigenomics", the impact of which may be equal to or greater than that of pharmacogenetics. We provide here an overview of this potentially major new field in pharmacology and medicine.

Introduction

Definition of epigenetics

The word "epigenetics" has had many definitions, and its meaning has changed over time. Initially it was used in a broad sense, but has become more narrowly linked to specific molecular phenomena occurring in organisms [1]. Epigenetics, as in "epigenetic landscape", was first coined by Waddington in 1942 as a portmanteau of the words "genetics" and "epigenesis" [2]. "Epigenesis" is an older word used to describe the differentiation of cells from their initial totipotent state in embryonic development. When Waddington coined the term, the physical nature of genes and their role in heredity was not yet known, so he used it as a conceptual model of how genes might interact with their surroundings to produce a phenotype. Holliday subsequently defined epigenetics as "the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms" [3].

The modern usage of the word is narrower, referring to heritable traits in cells and organisms that do not involve changes to the underlying DNA sequence [4]. The Greek language prefix "Epi" denotes features that are "above" or "in addition to" something; thus epigenetic traits exist on top of, or in addition to, the traditional

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molecular basis for inheritance. Hence the modern meaning of "epigenetics" basically refers to changes in gene expression in cells and organisms. These changes may persist through cell division and for the remainder of the cell's or organism's life. Sometimes the changes last for multiple generations of the organism, and are known as "transgenerational" effects [5], but again, there is no change in the underlying DNA sequence. Rather, environmental factors cause the organism's genes to behave, or "express themselves", differently [6]. A good example of epigenetic change is the process of cellular differentiation. During morphogenesis, totipotent stem cells become the various pluripotent cell lines of the embryo, which in turn become fully differentiated cells [7,8]. In other words, a single fertilized egg cell, the zygote, changes morphology over multiple divisions into the many cell types of the organism, such as neurons, liver cells, epithelium, blood vessels, etc., as it continues to divide. It does so by a process of activating some genes, while silencing others [7,8]. Regenerating totipotency during development of germ cells or nuclear transfer (cloning) entails re-expression of pluripotency-specific genes and extensive erasure of epigenetic modifications [8].

The similarity of the word to "genetics" has generated many parallel usages. The "epigenome" is a parallel to the word "genome", and refers to the overall epigenetic state of the genome. The phrase "genetic code" has also been adapted to the "epigenetic code" and has been used to describe the set of epigenetic features that create different phenotypes in different cells. Likewise "genomics" becomes "epigenomics", the study of epigenetic modification at a level much larger than a single gene, including whole-genome epigenetic scanning technologies, and the detection of quantitative alterations, multiplex modifications, and complex regulatory sequences outside of genes [9].

Relevance of epigenetics to modern medicine

In the past few years, several pioneering studies have brought epigenetics to the forefront of molecular biology, and this rapidly growing field has been the subject of several excellent reviews [6,10–13]. Interest has dramatically increased as it has become clear that epigenetics will be essential to understanding many topical biological phenomena such as stem cells [14], nuclear transfer (cloning) [15], cellular reprogramming [16], aging [17], evolution and speciation [18], and agriculture [19].

Also, it is becoming clear that a wide variety of common illnesses, behaviors, and other health conditions may have at least a partial epigenetic etiology, including cancer, respiratory, cardiovascular, reproductive, and autoimmune diseases [10], neurological disorders such as Parkinson's, Alzheimer's, and other cognitive dysfunctions [10,20], psychiatric illnesses [21], obesity and diabetes [22], infertility [23] and sexual dysfunction [24]. Effectors of epigenetic changes include many agents, such as heavy metals, pesticides, tobacco smoke, polycyclic aromatic hydrocarbons, hormones, radioactivity, viruses, bacteria [10], basic nutrients [25], and the social environment [26], including maternal care [27]. It has even been suggested that our thoughts and emotions can induce epigenetic changes [28,29].

Disease nosology as a "fuzzy" concept within an epigenetic framework

Exactly how the environment changes gene expression at the molecular level and how this can lead to disease are being explored in novel approaches to environmental health research [6,30]. Indeed, the very definitions of health and disease may be redefined, or at least blurred, when considered in an epigenetic context, since the boundary between the two states is obviously not a strict one, but rather "fuzzy" when considered from the perspective of gene expression [31]. Epigenomic studies will thus further the development of theories concerned with the application of non-Aristotelian concepts (that violate principles of classical logic) to the diagnosis and nosology of illness [32,33]. And high-throughput epigenetic screens will surely have an enormous impact on understanding the causes of "complex" non-Mendelian disease [34–37]. For example many "Functional Somatic Syndromes" such as chronic fatigue syndrome, post-traumatic stress disorder, fibromyalgia, 'sick building syndrome', chronic Lyme disease, etc. that are currently hard to diagnose, medically explain, and treat because they are outside the traditional model of disease as a single entity, might only be understood at the mechanistic level by applying concepts of systems biology and epigenetics [38,39].

A diverse variety of epigenetic processes have been identified

Many types of epigenetic processes have been identified, such as methylation of DNA [10], and acetylation, phosphorylation, ubiquitylation, and sumolyation of histones [10]. Other types of regulation that might be termed epigenetic, since they provide an extra layer of transcriptional control are: gene translocation, DNA repair, RNA transcription, RNA stability, alternative RNA splicing, protein degradation, gene copy number, and transposon activation [30]. Recently the effects of miRNAs on epigenetic machinery, and the control of miRNA expression by epigenetic mechanisms have been explored [40]. Other epigenetic mechanisms are likely to be discovered as research advances.

In summary: epigenetic processes are natural and essential to the function of organisms, but if they occur improperly, there can be major adverse health and behavioral effects.

The hypothesis

Although it is now becoming well-established that various environmental agents can cause epigenetic changes, one class of compounds that has been largely absent from most studies so far, is pharmaceutical drugs. Based on our rapidly-accumulating knowledge of gene/environment interactions, it stands to reason that drugs in current therapeutic practice would affect the epigenomic state of genes.

Therefore, the fundamental hypothesis of this article is that commonly-used pharmaceutical drugs can cause persistent epigenetic changes, which can be manifested in the persistence of drug-induced adverse events (side-effects). Below we evaluate the evidence for this hypothesis, and discuss the consequences for modern medicine should it prove to be correct.

Evaluation of the hypothesis

Here we provide examples of drugs for which there is clinical and/or experimental evidence for epigenetic effects as a direct effect on DNA methylation or histone acetylation, or indirect effect on transcription factor activation or receptor expression, etc. We also consider drugs which have been documented to cause persistent side-effects, but for which an epigenetic etiology for such effects has yet to be proven. A full list of drugs described here, with their attendant known or postulated epigenetic effects and/or side-effects is shown in Table 1.

Direct effects

Hydralazine, procainamide, valproate, and methotrexate

Some drugs which had an unknown mechanism of action when they were first introduced are now known, remarkably, to effect DNA methylation or histone acetylation. Two examples of the former are the drugs hydralazine, a vasodilator used to treat