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California Cornflakes and Brown Sugar: The Genetic Predisposition to Heroin and Cocaine Addiction

Society generally views drug addicts with contempt, regarding them as worthless and unproductive, products of irresponsible decisions. Addicts are not functional members of the population because the work involved in obtaining, using, and protecting their stash consumes their lives. Twenty-three per cent of state prisoners readily admit to being current heroin users (Vital Heroin Statistics.) Drug addicts also incur very high overall medical costs because of secondary illnesses such as hepatitis C, HIV/AIDS, and other types of infections. Normally, these people are outcasts, considered the dregs of society. However, newly emerging genetic evidence may help to combat this debasing stigma. Epidemiological studies show that around 40-60% of the risk of developing an addiction to heroin is genetically determined (Kreek, M.J. *et al.* 2005). Despite the complexity of these phenotypes, genome-wide association studies along with candidate gene case-control association studies have identified genetic markers and genotype patterns that identify increased risk of opiate and cocaine addiction for an individual. Not only are these findings extremely important from a preventative standpoint, but perhaps in the future, pharmacodynamics and pharmacokinetics will contribute to the provision of specific treatments for particular genotypes.

Substance abuse rarely occurs in isolation. Instead, it most often appears in conjunction with a complex psychiatric condition such as depression, anxiety, antisocial personality disorder, or attention deficit/hyperactivity disorder (Rousanville, B.J. *et al.*

1982). In epidemiological studies, 20-50% of stimulant or opiate addicts have depressive and/or anxiety disorders (Rousanville, B.J. *et al.* 1982.) Therefore, it is extremely difficult to distinguish and separate the addictive phenotype from the behavioral disorder. Both need adequate and appropriate treatment in order to have a successful recovery program. Vulnerability to addiction results from the interplay between environment (including stress and other psychiatric disorders), drug induced factors (how the drug changes the brain's chemistry), and genetic factors.

Indirect Genetic Factors: The Predisposition to Having an Addictive Personality

Evidence that personality traits could have their own genetic basis is mounting, and certain personality traits, such as impulsivity, lack of inhibitory control, and risk taking predispose a person to experimenting with drugs. Thus, researchers are starting to challenge the popular notion that drug addiction is the outcome of poor choices.

Additionally, at each stage in the addiction process, there are different magnitudes to which environment and genetics influence an individual. These are most apparent in the transitions from initiation of use to regular habit, from habit to dependence and from sobriety to relapse.

Impulsivity and novelty seeking are the personality characteristics most commonly associated with the initiating event of drug use and can lead to addictive behaviors. These traits are analogous to the shotgun signaling the beginning of a race – without it an individual would never have started running in the first place. Early candidate gene studies on impulsivity tied this trait to TPH1, which codes for the rate-limiting enzyme in the production of serotonin (Kreek, M.J. *et al.*, 2005.) TPH1 has also been associated with aggression and suicide. The transition from occasional use to

addiction may be correlated to risk-taking personalities, which in turn have been associated with a DRD4 polymorphism in dopamine receptors (Kreek, M.J. *et al*, 2005.) The discovery of these types of connections could dramatically change society's perceptions about drug addicts. While this kind of research is still in its infancy, additional consistent findings could be used to alter public opinion and to educate the public about heroin addiction. Seen as a biological consequence of certain genetically-based personality traits, heroin addiction loses its overwhelmingly negative connotation as a deviant behavior and can be viewed as a complex disease.

Addiction and the Brain

The mesolimbic dopaminergic pathway is the neural mechanism that regulates mood intensity. A good mood is the result of more dopamine flooding the synaptic cleft. Dopamine is the pleasure hormone that is associated with feelings of euphoria, and inhibitors keep it in careful check. Opiates indirectly cause dopamine neurons to release their dopamine. By inhibiting the dopamine inhibitors, opiates stimulate the activity, allowing dopamine to rampage without control throughout the brain. Mu opioid receptors are the inhibitors, which, under normal circumstances, are unlocked with the endorphin key. This lock and key method changes the shape of the receptor sign sent to the cell. The signal causes a chemical change, which in turn signals the release of neurotransmitters. Opiates take the place of natural endorphins and continually over stimulate the brain with excess dopamine. The brain builds up a tolerance to opioids and so becomes less sensitive to them over time. This begins the addiction cycle because increasingly higher levels of heroin are required to feel normal, and excessive amounts are needed to achieve

the ever elusive “high.” When heroin is withheld, withdrawal symptoms are intense and painful.

Direct Genetic Factors: OPRM1

The mu opioid receptor (G protein coupled receptor for beta endorphin) is the main target for heroin and opioid analgesia. This receptor plays a pivotal role in determining opioid tolerance and addiction. The gene which codes for this receptor is the OPRM1 gene, and studies have found a distinct connection between OPRM1 and opiate dependence.

The 118G allele of A1186 single nucleotide polymorphism (SNP) mutation is positively associated with heroin abusers (Yuferov, V. *et al* 2010.) It is the most studied polymorphism of the OPRM1 gene. The variant 118A→G removes the N glycosylation site in OPRM1 extracellular domain. With this loss of a glycosylation site, the 118G allele has less abundant expression than the 118A allele. This mutation is correlated with the loss of OPRM1 function. In addition, the 118A→G modification is associated with the pharmacogenetics variability morphine response, as was shown by differences between pain cores and self-administered morphine amounts.

The two strongest signals of heroin addiction in an individual (as found in genome-wide association studies) are variants rs510769 and rs3778151 (Levrán, O. *et al*, 2008.) These two SNPs are located in non-coding regions of intron 1 of the OPRM1 gene. The function of these SNPs is purely theoretical currently, but it has been proposed that this intron might create a heterodimer with the OPRM1 modulator. In addition, there is a haplotype association in this same region. In rs510769-rs3778151, if the haplotype CT is present, then the effect is actually protection from heroin addiction. In contrast, if

in rs510769-rs3778151 the haploype TC is present, then an individual is at greater risk of becoming addicted to heroin (Levrán, O. *et al*, 2008.)

Epigenetic modification is equally influential on end products of a gene because it helps to control transcriptional regulation. Studies show that heroin addicts have a significantly higher methylation of the OPRM1 gene promotor 2116 Cp6 site than normal individuals have (Yuferov, V. *et al* 2010.) This hypermethylation reduces the expression of the OPRM1 gene, further heightening the effects of heroin in the neural network. What causes this hypermethylation is unclear. It could be a result of the increased presence of heroin; it could merely be an imprinting error causing greater susceptibility to heroin addiction; or it could have been caused by earlier life events that happened prior to exposure. These questions highlight the difficulties of working with such a complex disorder as heroin addiction.

Direct Genetic Factors: OPRK1

The kappa opioid receptor (KOPr) plays a major role in the dopaminergic nigrostriatal/mesolimbic mesocortical systems. KOPr binds the peptide dynorphin as its primary ligand. Together, the dynorphin-KOPr system may be integral to the brain's countermodulatory mechanisms of the post drug-induced dopaminergic stimulation. Interfering with this response may increase cocaine dependence. Dynorphin inhibits dopamine release, which in turn inhibits cocaine's euphoric effects. K-Opioid agonists, primarily dynorphin, are thought to be the body's natural addiction control mechanism. Ongoing research into this agonist seeks to determine whether it could be useful in the treatment of addiction. A positive association was found between a 68 base repeat polymorphism in the promotor of the dynorphin gene and cocaine abuse/dependence

(Kreek, M.J. *et al*, 2005.) This mutation induces lower levels of transcription of the gene, so individuals with this phenotype are more susceptible to the effects of cocaine and are more likely to become dependant. The OPRK1 gene codes for the kappa opioid receptor which is found on chromosome 8q11.2. Studies found that 36G→T SNP exhibited significance with cocaine abuse and cocaine/alcohol dependence. In addition, the variant rs6473797 in intron 2 of OPRK1 was positively associated with individual protection from cocaine dependence (Yuferov, V. *et al* 2010.) One study found that haplotype CCT instead of TTC (the more common haplotype in European American subjects) was associated with a risk for developing cocaine dependence (Yuferov, V. *et al* 2010.) The positive associations of addiction with the mu and kappa opioid receptors further reinforces the importance of these two systems in the neurobiology of reinforcement and reward by certain drugs (Kreek, M.J. *et al*, 2005.)

Poly-Substance Abuse: COMT

Catechol-O-Methyl Transferase is an enzyme that degrades catecholamines such as the important neurotransmitter dopamine. The COMT gene encodes this protein. The most common SNP is the Val158Met polymorphism. The substitution of 472G→A results in a fourfold decrease of activity of COMT (Yuferov, V. *et al* 2010.) This mutation, resulting in a methionine amino acid, lowers the final enzymatic activity of the transferase. The Val allele version can hydrolyze dopamine much faster after a neurotransmitter activity, reducing overall dopaminergic stimulation. The 158Val→Met polymorphism is highly correlated with polysubstance abuse, with alcoholism, and with heroin addiction in Chinese and European American populations (Szeto, C. *et all*, 2001.) This is because the 158Met mutation results in lowered COMT activity and increased

dopamine availability, leading therefore to larger responses in the prefrontal cortex in anticipation of reward than the 158Val genotype.

Current Addiction Treatment vs. Future Pharmacogenetics

Various medications are used to lessen the discomfort and to combat the sharp withdrawal symptoms produced when reducing the use of such addictive drugs as heroin or cocaine. The most effective treatment for heroin withdrawal is methadone because it occupies the mu opioid receptor protein. However, it is a much more stabilizing factor because it permits the addict to normalize his own behavior and to discontinue the use of heroin. Methadone equalizes the sharp highs and excessive lows common to heroin abuse. If a patient on methadone relapses, it can remain an isolated event as dependent behaviors are less likely to return. This treatment allows for normalization of psychological abnormalities. However, there are no pharmacological treatments for cocaine addiction at this time.

Variants of genes that specifically encode the metabolism of opiates and cocaine are being targeted currently for future treatment of addiction. Because individuals have different genotypes, they have slightly different vulnerabilities to certain drugs. In the future, doctors may be able to utilize and manipulate their knowledge of genotypes to tailor treatments with increasing efficiency and higher levels of recovery.

In addition, standardization of phenotypes is needed to provide more concrete results. Differences in age of initiation, speed of progression to addiction, severity of dependence/withdrawal, and vulnerability to relapse are important variables to identify and differentiate for each person. Delineating certain boundaries of addiction may aid researchers in finding more concrete and helpful genetic results.

Conclusion

The most important consequence of this research is the validation of the proposal that heroin/cocaine addiction is a legitimate disease. Becoming an addict is not entirely a free choice but instead is driven by a disorder of brain chemistry. Reinforcing this notion may help to remove the stigma of addiction and to reintegrate recovering addicts more effectively into society. Addiction results from a complex interplay between genes and environment. Therefore, if there truly is a war on drugs in this country, it must be fought on two battlegrounds. There are steps that the general public can take that do not require an extensive understanding of biochemistry. Various community outreach programs can address social and economic factors such as the availability of drugs and the despair of poverty. While the environmental battle rages on in the public sector, biochemists will continue to seek to understand more completely the genetic contribution to this complex and emotionally loaded term, “addiction.”

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