# Addressing Addiction: A Look at How Addiction Functions at the Levels of Science and Society

Biochemistry 158

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**Introduction**

As a student progressing from high school to college, I knew that I loved to study biology because of its comprehensive yet unending scope of detail. Studying mammalian physiology and anatomy was akin to a philosophical self-realization. What more could I want? With each biology course, I unraveled more and more knowledge of myself and the living systems. In this genomics class, I learned about the power of comparing personal genetics and how that often leads to better understanding of diseases and determining susceptibilities of disease for individuals. Yet again, this new understanding excited me, but I kept arriving at particular knots of uncertainty. These knots were the social implications of such knowledge. I had previously written about addiction, and learning about its mechanisms made me wonder how this new knowledge was applied in rehabilitation in our society. So with this final paper, I'd like to further delve into the intersection of addiction's genomics, mechanisms, and social implications.

Addiction involves manipulation of the brain's reward and memory systems. These systems help reinforce behaviors and motivations that would improve an organism's survival and well-being. In a primal sense, survival means finding enough food, finding a mate, and staying alive. Beneficial behaviors are reinforced by perceptions of pleasure and happiness, and in contrast, aversion is mediated by perceptions of pain. For humans, recreational drugs overstimulate the reward systems in a way that leads to addiction, so in a sense, substance abuse hijacks the rewards and memory systems. These issues become relevant to me when considering those in my community who are dealing with various types of addiction. In my family, alcohol, cigarettes, and gambling are inherent to the old Vietnamese culture. Opioid and amphetamine addictions plague those in the streets around me. Substance abuse has shaped much of my environment, and being able to understand it makes me feel empowered to contributing to the

progressing development of such issues.

With increasing efforts towards research and reform of drug abuse, our society has been able to address drug addiction as something beyond its negative and static stigma. Addiction (in many realms of human habit) can now be partially attributed to an individual's inherent genetics, not just social or economic influences. That perspective is empowering, because it enables progress and an attitude towards finding solutions instead of sweeping problems under the rug. The application of science and research to a social problem creates legitimization and investment in a widespread problem. That being said, genetics has helped to break down the barriers to understanding addiction at a scientific level, but the application of these solutions is far from basic science. True success in addressing addiction requires effort from the government and public. This involves adjusting federal funding, health care considerations, and public attitudes, bridging the gap between two people who could suffer from the same addictions but face different outlooks in life due to circumstance.

**I. Genetic Associations**

For a previous assignment for this class, I reviewed several genome-wide association studies (GWAS) of different drug addictions. I will later explore the functional implications of the respective genetic variations.

Amphetamine addictions were found in association to a variety of genes. In one study, amphetamine addiction was associated with the cadherin 13 (CDH13) and SRD5A1 genes (Hart 2012). Cadherin 13 is expressed in many brain regions and in parts of the body, so the mechanism of its variation is ambiguous for amphetamine addictions. Variations of CDH13 have been found in other GWAS for methamphetamine, nicotine, and alcohol dependence (Drgn et al.

2009, Uhl et al. 2008, Treutlein et al. 2009). In this study, the positive association had a minor allele frequency (MAF) of 22% with the variant SNP rs3784943, which occurs in the eighth intron of CDH13. For the SRD5A1 gene, the variant SNP rs472402 had a MAF of 46%. SRD5A1 is expressed throughout the brain, with highest expression in the cerebral cortex, hippocampus, thalamus, hypothalamus, and amygdala (Roselli et al. 2011).

A study of heroin addiction found association with genes that encode the mu, kappa, and delta opioid receptors (Levran et al. 2008). The mu opioid receptor is encoded by the OPRM1 gene, and two significant variants were rs510769 (p-value = 0.0008) and rs3778151 (p-value = 0.003). Both SNPs occur in the first intron of OPRM1, which is on chromosome 6. The kappa opioid receptor is encoded by OPRK1, and one significant variant was rs6473797 (p-value = 0.004), which occurs on the second intron of OPRK1 on chromosome 8. The delta opioid receptor is encoded by the OPRD1 gene on chromosome 1, and three significant variants were were rs2236861 (p-value = 0.002), rs 3766951(p-value = 0.009), and rs 2236857 (p-value = 0.008). All three variants of OPRD1 occur on the first intron of OPRD1.

These GWAS associations reveal genetic variations that influence protein function and can therefore make individuals more susceptible to addictive behaviors.

**II. Functional Implications**

The genetics of addiction are important in proving the heritability of such a disease. What do these genetic variations mean on a functional level?

In the brain, there is high expression of genes that encode cell adhesion molecules, which are important in neuronal axon development. In general, cell adhesion genes are relatively large and therefore more prone to allelic variation (Drgon et al. 2010). CDH13 is part of the cadherin

family, which is a group of calcium-dependent cell adhesion proteins that have homophilic interactions (Purves 2004). One study suggests that CDH13 functions as a negative regulator of neural cell growth (Takeuchi et al. 2000), but I have yet to find a clear mechanism of how and where CDH13 operates within a neuron. CDH13-knockout mice have been reported with decreased conditioned place preference for cocaine (J. Drgonova unpublished), so along with the aforementioned associations with other addictions, there is evidence that CDH13 has some role in mediating the reward or memory systems. Genetic variants of CDH13 may either impair or overexpress the protein function, compromising the neural networks that influence behavior.

The SRD5A1 gene encodes an enzyme that catalyzes the conversion of progesterone to allopregnanolone. This suggests in the endocrine system, but in the brain, allopregnanolone is a $GABA_A$ agonist which causes mild sedative effects in humans. In other study, SRD5A1 was a candidate gene in studying cocaine dependence and major depressive episode (Yang 2011). Variants of SRD5A1 may result in an overactive enzyme, causing greater sedative effects from amphetamine use.

Opioid receptors are G-protein-coupled receptors with opioids as their ligands, and these receptors are components of the reward, drug craving, and relapse (Levran). Researchers described the minor allele variants as affecting either risk of or protection from addiction. The mutations of mu and delta receptors increase risk of addiction, and mutations of the kappa receptor can compromise protection from addiction. Activation of the mu opioid receptor can result in euphoria, analgesia, and sedation, which are desirable effects of heroin use. The delta opioid receptors cause analgesia, emotional response, and increased pain tolerance. Variations of these two receptors can increase their effects and increase the desire for individuals to try heroin again. The kappa opioid receptor modulates dopaminergic tone and can actually oppose effects

of the mu opioid receptor. Variations of this receptor may inhibit its regulatory effect on the reward system and therefore increase individual desire to try heroin again.

These functional implications are not direct causes of substance addictions, but they reveal how genetic variations can make some individuals more prone or vulnerable to addiction than others. Addiction is a multifactorial process, which requires treatments at different steps to have effective prevention and rehabilitation.

**III. Addiction in the Scope of Society**

My passion meets with frustration at the societal level of addiction. It is indeed fulfilling to understand the genetic and anatomical vulnerabilities of addiction, but what of the applications? When considering genetic testing and pharmacological drug treatments, a financial hurdle materializes for many people. It will be a long time before such a standard of health care will be affordable for the masses. The marginalized populations in our society will hardly have the chance to even access this degree of knowledge and understanding, never mind the treatments. This is in consideration of the low-income and homeless communities, people who are often without health insurance and its resources. Pathways of harm reduction and rehabilitation have to be constructed with federal and state-mandated aid, and then the welfare of these populations can be better prioritized in our communities.

To ensure success of rehabilitation from addiction, a number of studies have shown that additional social services are needed. Social services are especially critical for low-income or homeless persons, because it is often their socioeconomic circumstances that prevent them from getting clean. This reflects the community reinforcement approach (CRA) to treating substance abuse and addiction (Meyers and Miller 2001). The CRA emphasizes that drug and substance problems are best addressed with changes in the person's environment and lifestyle. It was only

until the 1970's that the United States government drafted the Uniform Alcoholism and Intoxication Treatment Act to decriminalize public drunkenness. It promoted longer-term solutions for chronic drinkers and reduced the "revolving door" issue of cycling chronic drinkers in and out of jail (McCarty et al. 2007). The U.S. has progressed since then, with the Affordable Care Act emphasized in the 2012 White House National Drug Control Strategy. The act requires that insurers expand coverage for disorder treatment services, which enables access to rehabilitation for more people.

One study examined the effectiveness of social services in addition to standard addiction rehabilitation (Mclellan et al. 1998). The additional social services were medical screenings, housing assistance, parenting classes, and housing services. With six months, researchers found no significance difference in improvements from addiction, but after 12 and 26 months of treatment, they found reduced substance abuse, improved physical and mental health, and better social function in the group with social services.

Another study found that housing was associated with a higher prevalence of drug abstinence for homeless substance abusers (Milby et al. 2005). The participants were homeless persons with cocaine dependence and nonpsychotic mental disorders, and all participants received access to therapy groups and individual counseling. Housing was either abstinence-contingent or non-abstinence-contingent, and housing also offered an income opportunity via work therapy. Other studies support this finding that long-term abstinence can be better implemented with social services that enable behavioral changes (Higgens et al. 2000, Rawson et al. 2002). Another interesting detail was that the group with abstinence-contingent housing had a slightly higher prevalence of drug abstinence compared to the group with non-abstinence-contingent housing. Researchers of that study note that some authorities would prefer non-

abstinence-contingent housing, because it would be cheaper without the costs of monitoring drug use and ejecting participants from housing. This brings up the compromise between federal aid and treatments that are "good enough" for populations can't otherwise afford them. It feels that this balance will be a continual issue to oversee because of the controversies in providing aid to a marginalized population in society.

**Concluding Remarks**

Unraveling these many aspects of drug addiction hasn't necessarily brought me to conclusive answers. There are still gaps in the understanding of how certain proteins function and how neural circuits associate. The community is still progressing with its attitude towards the ethics and morals of substance abuse. The legal system, financial aids, and social services are still coordinating to meet the health standards that are determined by the community. And throughout all of this progression, these different areas of knowledge have to collaborate to improve addiction as it exists today.

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