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Niki Hosseini-Kamkar
UWO

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The A1 Allele of the Taq1 A Polymorphism in Association with Addiction: A Review

Niki Hosseini-Kamkar*

Substance abuse occurs when individuals move from voluntary drug use to compulsive drug use despite significant costs to their social, psychological, and physical well-being. Considering the adverse effects of compulsive drug use, an investigation of biological and environmental factors that make individuals susceptible to addiction becomes very useful. This paper will investigate one possible biological factor that influences addiction, specifically, I review the literature on the A1 allele of the Taq1 A polymorphism of the DRD2 gene. The literature on the association between the A1 allele with alcoholism reveals that the A1 allele is more prevalent in alcoholics versus non-alcoholics. However, the A1 allele does not seem to be a susceptibility factor specific to alcoholism, but it may be associated with a predisposition to addictive and impulsive behaviours in general. Next, the literature on the association between the A1 allele and addictive and impulsive behaviours in general will be reviewed. In addition, this paper attempts to find a theoretical framework that explains the A1 allele's association with addictive and impulsive behaviours. In doing so, I will discuss the hypodopaminergic hypothesis and how the A1 allele may make individuals susceptible to experiencing a hypodopaminergic state. The hypodopaminergic hypothesis states that individuals who are predisposed to addiction have reduced dopamine (DA) levels (a hypodopaminergic state); and in order to alleviate this hypodopaminergic state, they are motivated to seek positive reinforcers in an attempt to increase DA levels. I review evidence that supports the hypodopaminergic hypothesis by demonstrating an association between the A1 allele and inefficient D2 receptor functioning. This inefficient D2 receptor functioning may lead to a hypodopaminergic state that motivates individuals to seek drugs and other addictive behaviours to increase DA levels.

Addiction involves a transition from voluntary to compulsive drug use despite adverse psychological, social, and physical consequences (Everitt et al., 2008**).** Considering the adverse consequences of compulsive drug use, it is important to investigate possible biological factors that may make individuals susceptible to addiction. Neurons are nerve cells that comprise the basic building blocks of the nervous system. Neurons produce neurotransmitters—chemical substances that carry messages to either excite or inhibit the firing of other neurons. Neurotransmitters exert their influence on neurons by binding with or attaching to receptors that are large protein molecules embedded in the receiving neuron's cell membrane (Passer, Smith, Atkinson, Mitchell, & Muir, 2005). Dopamine (DA) is a neurotransmitter that plays a central role in motivation, cognition, locomotion, and reward-seeking behaviours (Bannon, Michelhaugh, Wang, & Sacchetti, 2001). In addition, dysfunctions of the dopaminergic system have been implicated in numerous neurological and psychiatric disorders, including drug abuse, schizophrenia, affective disorders, attention deficit hyperactivity disorder (ADHD), obesity, pathological gambling, and post-traumatic stress disorder (PTSD) (Blum et al., 1994). The central role of DA in reward-seeking behaviours makes DA and the genes involved in DA synthesis, degradation, and receptor production suitable candidates for the investigation of the molecular basis of addiction (Bowirrat & Oscar-Berman,

*Initially submitted for Psychology 3209F at the University of Western Ontario. For inquiries regarding the article, please email the author at *nikikamkar@gmail.com*.

2005). One gene of interest in susceptibility to addiction is the D2 dopamine receptor (DRD2) gene, which encodes D2 subtypes of DA receptors. The DRD2 gene may be associated with drug addiction because alterations in DA availability at its receptors have been implicated in reward mechanisms (Blum et al., 1991).Studies have shown that low D2 receptor availability is associated with a propensity to seek drugs. This greater propensity to self-administer drugs is potentially an attempt to increase the likelihood that DA will bind to the few receptors available. Therefore, a gene that may alter the amount of D2 receptors available is a candidate gene for the investigation of biological factors contributing to addiction (Blum et al., 1991).

The A1 allele of the Taq1 A Polymorphism Associated with Alcoholism

In 1990, Blum et al. conducted a study to investigate D2 receptor genes in alcoholics and non-alcoholics. Their experiment involved detection of restriction-fragment-length-polymorphisms (RFLPs) of the DRD2 gene; specifically, the researchers investigated the Taq1 A polymorphism in the DNA extracted from deceased alcoholics and a control population of non-alcoholics. A polymorphism refers to phenotypic or observable variability (poly = many, morph = form). A genetic polymorphism occurs when genetic variation results in a difference in phenotypic form. The DRD2 gene has a polymorphism in the noncoding region, called the Taq1 A polymorphism. There are four Taq1 A alleles (or genetic variants): A1, A2, A3, and A4. The A2 allele is the most common while the A3 and A4 alleles are rare (Blum, Cull, Braverman, & Comings, 1996). In the original Blum et al. (1990) paper, 35 alcoholics and 35 non-alcoholics were sampled. Of the alcoholics, 69% had the A1 allele; in contrast, only 20% of the non-alcoholics had the A1 allele (Blum et al., 1990). This was the first study to report an association between the A1 allele of the Taq1 A polymorphism and alcoholism.

The association between the A1 allele of the Taq1 A polymorphism with alcoholism has been replicated in numerous other experiments (Amadeo et al., 1993; Arinami et al., 1993; Hietala et al., 1997; Ovchinnikov et al., 1999; Pato, Macciardi, Pato, Verga, & Kennedy, 1993; Young et al., 2002). For example, Arinami et al. (1993) reported that the A1 allele was present in 77% of severe alcoholics versus 59% of less severe alcoholics. Simply put, there was a strong correlation between participants who were homozygous for the A1 allele and those who were classified as severe alcoholics. (Arinami et al., 1993). Note that an individual is homozygous for an allele when they possess two identical alleles for a trait (A1/A1 genotype). In comparison, heterozygous individuals possess only one copy of the allele (A1/A2, A1/A3, or A1/A4 genotype in the case of the Taq1 A polymorphism).

Amadeo et al. (1993) reported similar results with a sample of patients diagnosed with alcohol dependence (DSM-III-R criteria) in north west (NW) and south east (SE) France. These patients were compared to matched controls. The results revealed that the frequency of the A1 allele was significantly greater in the alcoholics (24.4%) compared to non-alcoholics (8%). Simply put, the A1 allele occurred more often in alcoholics versus non-alcoholics. In addition, the proportion of the presence of the A1 allele was significantly greater in alcoholics (42.8%) compared to non-alcoholics (16.2%). In other words, the presence of the A1 allele relative to the A2, A3 and A4 alleles was significantly greater in alcoholics. Furthermore, a meta-analysis of eight studies revealed a significant association between the A1 allele of the Taq1 A polymorphism and alcoholism. Additionally, the meta-analysis revealed that the increase in susceptibility to alcoholism associated with the A1 allele was correlated with severity of alcoholism (Pato et al., 1993). Based on the aforementioned studies, there seems to be an association between the A1 allele of the Taq1 A polymorphism and alcoholism. Interestingly, other studies suggest that the A1 allele of the Taq1 A polymorphism is not only associated with increased susceptibility to alcoholism but may be involved in other

addictive behaviours as well (Comings et al., 1996).

The A1 allele of the Taq1 A Polymorphism Associated with Addictive Behaviours

In addition to being associated with alcoholism, the A1 allele of the Taq1 A polymorphism may be associated with other substance abuse and addictive behaviours. For example, Noble et al. (1994) investigated the A1 allele in Caucasian smokers and ex-smokers. Their experiment revealed that the prevalence of the A1 allele was greatest for current smokers (45.6%), followed by ex-smokers (40.0%) and was the least prevalent in non-smokers (28.0%). Similarly, the A1 allele has been shown to be associated with tobacco use (Comings et al., 1996), cannabinoid addiction (Nacak et al., 2012), and a preference for psychostimulants among polysubstance abusers (Persico, Bird, Gabbay, & Uhl, 1996). That is, homozygosity for the A1 allele (A1/A1 genotype) was significantly higher in addicts compared to control subjects. In addition, the frequency of the A1 allele was significantly higher in addicts compared to control subjects (Nacak et al., 2012).

Other researchers have reported an association between the A1 allele of the Taq1 A polymorphism and addiction to pathological gambling and obesity. In a study conducted by Comings et al. (1996), 50.9% of pathological gamblers carried the A1 allele compared to only 25.9% of control subjects (the control subjects were screened to exclude drug and alcohol abuse). Furthermore, of the gamblers who participated in the experiment, those with more severe gambling problems (upper half of the Pathological gambling Score) were more likely to carry the A1 allele (63.8%). In contrast, only 40.9% of the gamblers with less severe gambling problems carried the A1 allele. In addition, 60.5% of the gamblers with comorbid substance abuse carried the A1 allele, in comparison to only 44.1% of the gamblers without comorbid substance abuse. Based on the evidence obtained from their study, the authors concluded that the A1 allele of the Taq1 A polymorphism plays a role in pathological gambling, and that this variant of the DRD2 gene may be a risk factor for impulsive and addictive behaviours (Comings et al., 1996).

Similarly, Noble et al. (1994) investigated the influence of the DRD2 gene on obesity. The authors reported that the A1 allele was present in 46% of obese subjects versus only 19% of control subjects. Noble et al. (1994) reported the following: parental history and later onset of obesity as well as carbohydrate preference were observed in subjects carrying the A1 allele. Finally, the authors reported that the prevalence of the A1 allele in probands carrying three risk factors (parental history, later onset of obesity, and carbohydrate preference) was observed in 85% of obese subjects (Noble et al., 1994). These findings suggest that the A1 allele is associated with obesity and furthermore, that the risk factors of parental history of obesity, later onset of obesity and carbohydrate preference are associated with the A1 allele.

The Hypodopaminergic Hypothesis—How the A1 allele May Make Individuals Susceptible to Addictive Behaviours

Based on the above research, it is evident that the A1 allele of the Taq1 A polymorphism of the DRD2 gene is associated with impulsive and addictive behaviours. One possible explanation for these findings is based on the hypodopaminergic hypothesis of drug addiction. The hypodopaminergic hypothesis states that dysfunctions of the mesocorticolimbic dopamine system may cause a hypodopaminergic state—a condition in which the brain has reduced, or less than normal levels of DA (Bowirrat & Oscar-Berman, 2005). In order to alleviate this hypodopaminergic state, individuals are motivated to seek drugs and other positive reinforcers to activate neurons involved in DA release (Bowirrat & Oscar-Berman, 2005). In other words, certain genetic factors may influence the mesocorticolimbic dopamine system causing below normal levels of DA, or a hypodopaminergic state. To alleviate this hypodopaminergic state, individuals partake in behaviours such as drug abuse or gambling to increase DA levels

because neurons in the mesocorticolimbic system release DA in response to rewarding behaviours. It is plausible that individuals with certain genetic polymorphisms, like the Taq1 A, may have a deficiency in or an absence of DA receptors. Blum et al. (2000) state that impulsive and addictive behaviours are based on a common genetic reduction in the D2 receptor. It is this inefficiency in the functioning of D2 receptors that may induce a hypodopaminergic state and ultimately lead to addictive behaviors (Bowirrat & Oscar-Berman, 2005). Next, the literature on the association between the Taq1 A polymorphism and inefficient D2 receptor functioning will be reviewed to provide evidence in support of this hypothesis.

The A1 allele of the Taq1 A Polymorphism Associated with Inefficient D2 Receptor Functioning

As stated previously, individuals with the A1 allele may have reduced D2 receptors causing them to experience a hypodopaminergic state. One mechanism that may explain how reduced D2 receptors may lead to a hypodopaminergic state is through their actions on the dopamine transporter (DAT). The DAT is a plasma membrane transport protein that is involved in the rapid reuptake of DA from the extracellular space. This is the mechanism by which DA is recycled via DAT; in other words, the DA transported back into the presynaptic neuron can be repackaged into vesicles (Bannon et al., 2001). The DAT is densely distributed in the striatum and nucleus accumbens and is the primary source of DA regulation in these regions (Gizer, Ficks, & Waldman, 2009). Kimmel, Joyce, Carroll, and Kuhur (2001) reported that in the striatum of rats, the D2 receptor agonists R-(-)-propylnorapomorphine hydrochloride (NPA) and quinpirole decreased the half-life of DAT. By extension, this would mean that D2 receptor agonists would increase DA indirectly through their effects on DAT. On the other hand, the D2 receptor antagonist eticlopride increased the half-life of DAT thereby decreasing DA levels (Kimmel et al., 2001). This evidence provides a possible mechanism by which reduced D2 receptors could lead to a hypodopaminergic state. Individuals with reduced D2 receptors may be susceptible to seeking drugs and other rewarding behaviours to alleviate this deficiency in DA. Increasing the amount DA through rewarding behaviours (i.e., drugs, gambling) can help alleviate the hypodopaminergic state by increasing the probability that DA will bind to the few receptors available.

To investigate D2 receptor density and affinity in patients with alcohol dependence versus controls, Hietala et al. (1994) used positron emission tomography (PET). The authors reported a trend for decreased striatal D2 receptor affinity and density in patients with alcohol dependence in comparison to control subjects; however, these results were not statistically significant. The authors then investigated the ratio between D2 receptor density and affinity. The binding potential of D2 receptors was significantly lower in alcoholics versus controls (Hietala et al., 1994). Specifically, the Binding potential (Bmax/Kd ratio) was 19.7% lower in alcoholics compared to controls (Hietala et al., 1994). Binding potential (Bmax/Kd) is the ratio of receptor density to affinity, receptor density being the number of receptors present per unit area and receptor affinity being the strength with which a substance binds to a receptor. The authors concluded that the lower Bmax/Kd ratio in alcoholics reflects a reduced accessibility for [11C]raclopride (a radiolabeled compound used in PET that acts as a D2 antagonist) to D2 receptors in the striatum (Hietala et al., 1994). Therefore, according to Hietala et al. (1994), the reduced binding potential observed in alcoholics provides evidence for the reduced strength of striatal D2 receptors in alcoholics.

Wang et al. (1997) conducted a similar experiment using PET and reported significant decreases in D2 receptor availability in the striatum of opiate-dependent subjects compared to controls. The authors concluded that individuals who had low D2 receptor levels were more vulnerable to drug self-administration (Wang et al., 1997). Dalley et al. (2007) also found reduced D2 receptor

availability in the ventral striatum of high-impulsive rats compared to non-impulsive rats; however, the authors reported that these effects are independent of DA release (Dalley et al., 2007).

Thompson et al. (1997) investigated the association between the A1 allele of the Taq1 A polymorphism with D2 receptor binding in the striatum. Their results revealed that individuals who were heterozygous or homozygous for the A1 allele had significantly reduced D2 receptor binding in the striatum compared to individuals homozygous for the A2 allele. That is, the presence of the A1 allele was associated with 30 to 40% reduction in D2 receptor binding (Thompson et al., 1997). This means that the DA released in the striatum was not exerting its influence to its fullest potential in individuals who possessed the A1 allele. Similarly, Ritchie and Noble (2003) reported that individuals carrying the A1 allele had significantly and approximately 49% fewer D2 receptors (Bmax) than individuals who were not carrying the A1 allele. However, binding affinity (Kd) did not differ between individuals with the A1 allele and those without the A1 allele (Ritchie & Noble, 2003).

Based on the aforementioned studies, it may be tempting to conclude that the A1 allele is certainly correlated with reduced D2 receptor density. However, it is noteworthy to mention that not all researchers have been able to replicate the association between the A1 allele and D2 receptor density. For example, Laruelle, Gelernter, and Innis (1998) failed to replicate the association between the A1 allele and lower D2 receptor expression. Laruelle et al. (1998) used single photon emission computerized tomography (SPECT) and [123I] IBZM (a DA antagonist used as the radioactive tracer in SPECT). In this experiment, [123I] IBZM binding potential was the same in individuals with the A1 allele as compared to noncarriers of the A1 allele. The authors reported that they observed an effect of age on binding potential, but no effect of schizophrenia or A1 allele on binding potential (Laruelle et al., 1998). In a review paper, Hitzemann (1998) concludes that D2 receptor density is a complex phenotype under the regulation of many genes—all of which have only a moderate effect size. Furthermore, gene by environment interactions must be investigated to fully understand the nature of a genetic polymorphism on a complex phenotype like D2 binding potential. However the studies that detect a correlation between the A1 allele and reduced D2 receptor density and affinity outnumber those that do not. As such, in general it seems as though the A1 allele of the Taq1 A polymorphism is likely associated with reduced D2 receptor density and affinity.

Based on the research summarized, it is reasonable to conclude that the A1 allele of the Taq1 A polymorphism is associated with susceptibility to alcoholism and other addictive and impulsive behaviours. However, the molecular mechanisms through which the Taq1 A polymorphism influences the phenotype of addictive-impulsive behaviours are poorly understood. Nonetheless, one possible explanation is provided by the hypodopaminergic hypothesis. The A1 allele is associated with reduced D2 receptor affinity and density. Thus, this deficiency in normal D2 receptor functioning could lead to a hypodopaminergic state in the brain. That is, individuals who carry the A1 allele of the Taq1 A polymorphism may have reduced DA levels as a result of reduced or inefficient D2 receptors. As such, these individuals may seek drugs and other rewarding behaviors to alleviate this hypodopaminergic state. Therefore, carriers of the A1 allele may be susceptible to addiction because they are motivated by a hypodopaminergic state to seek positive reinforcers that activate neurons involved in DA release.

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