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SM Journal of Neurology and Neuroscience

Short Communication

Global Evidence for the Key Role of the Dopamine D2 Receptor Gene (DRD2) and DRD2 Receptors in Alcoholism

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Article Information

Received date: May 21, 2017
Accepted date: May 24, 2017
Published date: May 26, 2017

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Keywords Reward deficiency syndrome; Dopamine homeostasis; Dopamine D2 receptor Gene; Addiction medicine; Gene therapy

Abstract

It has been over 27 years since Blum & Noble discovered the first association of the DRD2 A1 allele in severe alcoholism, suggesting reward as the real phenotype, not alcoholism. This has been acknowledged by an explosion of research in the arena of Psychiatric Genetics. To date, a PubMed search listed 6,839 studies (5-15-17). The A1 allele has been associated with substance use disorders other than alcoholism, including cocaine, nicotine dependence, polysubstance abuse and many Reward Deficiency Syndrome (RDS) behaviors substance and non-substance related. Certainly following extensive controversy, the emerging evidence suggests that the DRD2 is a reinforcement or reward gene. In fact, it could represent one of the most prominent single-gene determinants of susceptibility to severe substance abuse/reward deficiency. While, however, the environment through epigenetic impact and other genes, when combined, still play the larger role, targeting the DRD2 gene through the novel genetic rewriting of the DNA code at the mRNA level may hold the greatest promise to date for potentially "curing" the RDS phenotype.

Introduction

Even before the actual cloning of the Dopamine D2 receptor gene in 1988 [1], dopamine receptors were correctly classified into D1 and D2 subtypes on the basis of pharmacological and biochemical properties [2]. Specifically according to Bunzow, et al. (1) the D2 Dopamine Receptor (DRD2) interacts with guanine nucleotide-binding proteins to induce second messenger systems. Moreover, other members of the family of G-protein coupled receptors in a primary aminoacid sequence, are significantly similar and exhibit an archetypical topology, predicted to consist of seven putative transmembrane domains [1]. In 1989, Weiner & Brann mapped the distribution of a dopamine D2 receptor mRNA in rat brain [3]. They reported that the D2 receptor mRNA is abundant in the caudate, putamen, accumbens nucleus and olfactory tubercle and lower levels in the medial habenular nucleus, diagonal band, lateral septal nucleus, claustrum, dorsal endopiriform nucleus, and entorhinal cortex. Most importantly, in the mesencephalon, DRD2 receptor mRNA is abundant within the substantia nigra pars compacta and the ventral tegmental area. It is noteworthy that the RNA distribution and the ligand binding indicate that pre and postsynaptic D2 receptors located in the nigrostriatal, mesolimbic and mesocortical pathways originate from the same mRNA.

Grandy, et al. [4] found that a chromosome mapping panel, when probed with the rat D2 receptor cDNA identified a 15-kb EcoRI restriction fragment located on human chromosome 11. Specifically, a human genomic fragment, lambda hD2G1, was cloned using the rat cDNA. The last coding exon of the DRD2 receptor gene 16.5 kb of 3' flanking sequence is part of the lambda hD2G1.

The lambda hD2G1 was hybridized to a chromosome 11 regional mapping panel, and DRD2 located at 11q at the q22-q23 junction of chromosome 11. They also identified a polymorphism using TaqI RFLP.

Alcoholism and Dopamine

Alcohol as well as other drugs of abuse are reinforcing substances which activate the mesolimbic dopaminergic reward pathways of the brain [5]. It is well-known that many studies have demonstrated alcohol's reinforcing effects manifest from enhanced dopaminergic, GABAergic and opioid signaling and its caloric properties. In fact, recently Dobbs et al. [6] reviewed the literature and suggested that Dopamine D2 Receptors (D2Rs) are consistently emerging as a critical substrate in the etiology of some major psychiatric disorders. The consensus favors a central theory of Substance Use Disorders (SUDs), that postulates a reduction in D2R levels in the striatum as a central factor that determines vulnerability to abuse substances including but not limited to alcohol. These authors further indicate that compelling evidence for a critical role of striatal D2Rs in shaping basal ganglia connectivity, and point out that this connectivity is not limited, it occurs among neurons that do not express D2Rs. Along these lines, Volkow's group [7] reported on a new repeat polymorphism of the AKT1gene that predicts striatal aldopamine D2/D3 receptor availability, as well as, stimulant-induced striatal dopamine release in the healthy human brain. The AKTi repeat polymorphism is of consequence when one considers the role of the protein kinase AKT1 in dopamine neurotransmission. While these findings have relevance related to the hyperdopaminergia secondary to dopamine release induced by stimulants and psychosis, the AKT1 gene may also play a role in the acute actions of alcohol in human brain function. Reduced dopamine levels and decreased D2 Dopamine Receptor (DRD2) numbers have been confirmed in the brains of alcohol-preferring animals [8-10]. Moreover, Ding, et al. [11] found that activation of dopamine receptors in the nucleus accumbens shell, ventral pallidum or medial prefrontal cortex, but not the nucleus accumbens core, is involved in mediating the reinforcing effects of alcohol in the core posterior Ventral Tegmental Area (VTA). This finding is that the 'alcohol reward' neuro-circuitry consist, at least in part, of activation of the dopamine projections from the posterior VTA to the nucleus accumbens core, ventral pallidum or medial prefrontal cortex.

In other work from McBride's group [12] that determined the comorbidity of nicotine and alcohol abuse and dependence, they found a differential effect. The response to the stimulating effects of ethanol increased following repeated exposure of the posterior VTA to nicotine, whereas repeated exposure to ethanol did not alter the responses of posterior ventral tegmental dopamine neurons to nicotine. This finding supports the concept that nicotine may be a *gateway drug* [12]. Certain lessons that relate to alcohol intake can be learned from work directed towards cocaine of DB Kandel's team [13] regarding the molecular mechanism for a gateway drug. They found that response to cocaine increased with pretreatment of mice with nicotine. The responses were assessed both behaviorally and through synaptic plasticity in the striatum, a brain region critical for addiction-related reward. They reported that nicotine primed an enhanced response to cocaine by the activation of transcription of the FosB gene. Histone deacetylase was inhibited, which caused global histone acetylation in the striatum and possibly up-regulation of dopaminergic gene expression.

Also, it has been established in both animal models and humans that dopamine receptor agonists reduce alcohol consumption, whereas in general, antagonists show the opposite effect. In fact, Dyr, et al. [14], reported that the D2 agonist quinpirole caused a dose-dependent decrease in alcohol drinking in High-Alcohol-Drinking (HAD) line of rats. In contrast, however, Spiperone, a D2 antagonist increased alcohol intake. New approaches show that dopaminergic activation in the VTA-nucleus accumbens projections, as expected, reduces consummatory behaviors. In fact, phasic dopamine release in the nucleus accumbens stimulated in optogenetic studies may determine many aspects of drug and natural reward-related behaviors. Specifically, Mikhailova, et al. [15] reported that optogenetic tonic stimulation of VTA-nucleus accumbens dopamine release is sufficient to inhibit, for example sucrose and alcohol. Rewarding consummatory behavior may be inhibited by preventing this circuit from engaging in the phasic activity, thought to be essential for reward-based behaviors, as reported in ADHD [16].

Moreover, animal studies determined that Quantitative Trait Loci (QTL) in the chromosomal region proximate to the DRD2 gene is a "hot spot" for alcohol-related behaviors [17,18]. Interestingly, the work of Buck et al. [17], definitively mapped a QTL on Chromosome (Chr) 9 linked to the D (2) dopamine receptor gene. They investigated the DRD2, for hypothermic sensitivity to quinpirole (a D2 agonist), and identified a possible QTL in the same chromosomal region after repeated treatments for tolerance to quinpirole.

There are a plethora of human studies (PubMed 5-15-17, 1,681) that provide additional support for a connection between alcohol dependence and CNS dopaminergic function. Most recently, for example, Siciliano et al. [19] found that in alcohol prone C57BL/6J compared to avoiding DBA/2J mice, following one or two weekly cycles of chronic intermittent ethanol **(CIE)** exposure significantly induced an attenuated dopamine synthesis in the ventral striatum of C57BL/6J. The authors suggested that autoreceptor effects on dopamine synthesis are different in C57BL/6J and DBA/2J mice, and that excessive drinking associated with decreased dopaminergic activity. These findings dovetail with other work showing that C57BL/6J compared to DBA/2J mice have lower levels of brain methionine-enkephalin [20] and that one-year of drinking alcohol induced blockade of leucine-enkephalin in basal ganglia of alcohol-loving Golden Syrian hamsters compared to non-drinking controls [21]. The positive interaction between enkephalins and dopamine and alcohol intake is well-known [22].

In endocrinological studies, reduced dopaminergic activity has been found in the most severe and genetic types of alcoholics [23]. Moreover, Oberlin, et al. [24] reported that low D2 receptors induce a preference for immediate gratification (reinforcement) as measured by monetary discounting. Furthermore, brain imaging studies are similarly revealing a diminished dopaminergic tone in alcoholics [25]. It is well-established that striatal dopamine (DA) is increased by virtually all drugs of abuse, including alcohol [26]. Using PET imaging Oberlin, et al. [27] elegantly showed that even the flavor of beer provoked ventral striatal DA release and the response is strongest in subjects with a greater genetic risk for alcoholism. These facts coupled with earlier work from Blum's group shows that the pro-dopamine regulator KB220 variants significantly reduced AMA (against medical advice) rates in some studies involving alcoholism, opiate dependence and cocaine abuse [28-31]. Ongoing research into the effects KB220Z™

has repeatedly confirmed numerous clinical benefits to individuals with genetic and epigenetic antecedents of addictive, compulsive, and impulsive behaviors [32] and most recently improved resting state functional connectivity in animals [33].

As authors, we are cognizant that risk for relapse has now been linked to hypodopaminergic genetics [34]. The super sensitivity to DA regarding relapse has been the subject of many articles. Here the hypothesis is that relapse to psychoactive drugs is due to a process called *deprivation-amplification* [35,36]. Polymorphisms of the D2 gene and low D2 receptor density are associated with a greater risk for relapse to substance abuse, including nicotine sensitization, alcohol and cocaine dependence, heroin and glucose craving and methamphetamine abuse. This is supported by the work of Dahlgren et al. [34] who found when compared to ***Taq A2*** allele carriers with alcohol dependence, carriers of the ***Taq A1*** allele with a dopamine D2 receptor gene relapse at a significantly higher rate. Additionally, alcohol-dependent subjects with the ***Taq A1*** allele have a significantly increased mortality rate [37].

Historically, the concept that low dopaminergic function is linked to substance and non-substance-seeking behavior is well known, and this idea dates back to the *dopamine depletion hypothesis* espoused by Dackis and Gold [38] to explain cocaine relapse. Others have indicated that the dopamine D2 receptor *Taq A2* allele is protective and carriers have diminished risk for all RDS behaviors [38]. Moreover, pharmacological, electrophysiological and neuropsychological studies have found a diminished central dopaminergic function in DRD2 A1 allele subjects [39-42]. Furthermore, treatment of alcohol dependence with adopamine receptor agonist showed more salutary effects on those who carry, rather than those who do not carry the DRD2 A1 allele [43]. Specifically, Noble's group [43] performed a a double-blind study placebo-controlled study of bromocriptine, a DRD2 agonist, administered to subjects with alcohol dependence with either the **A1** (A1/A1 and A1/A2) or the **A2** (A2/A2) allele of the DRD2 gene. Decrease in craving and anxiety occurred in the bromocriptine-treated **A1** alcoholics and attrition was highest in the placebo-treated **A1** alcoholics.

Summary

It has been over 27 years since Blum & Noble discovered the first association of the DRD2 A1 allele and severe alcoholism, suggesting reward as the real phenotype not alcohol dependence. This has been acknowledged by an explosion of research in the arena of Psychiatric Genetics. To date, a PubMed search listed 6,839 studies (5-15-17). The A1 allele has also been associated with SUDs other than alcohol dependence, including cocaine, nicotine dependence, polysubstance abuse and many other Reward Deficiency Syndrome (RDS) behaviors substance and non-substance related. Certainly following considerable controversy, the evidence suggests that the DRD2 is a reinforcement or reward gene. In fact, it could represent one of the most prominent single-gene determinants of susceptibility to severe substance abuse-reward deficiency. Other reward genes play a large role and environmental epigenetics further impact RDS behaviors by targeting the DRD2 gene through novel genetic rewriting of the DNA code at the mRNA level may hold the greatest promise to date for potentially "curing" the RDS phenotype.

Acknowledgement

The authors appreciate the expert edits of Margaret A. Madigan and the superb assistance of Mary Hauser of Dominion Diagnostics, LLC.

Funding

Rajendra D Badgaiyan is supported by the National Institutes of Health grants www.ncbi.nlm.nih.gov/ 1R01NS073884 and 1R21MH073624. Panayotis Thanos is the recipient of R01HD70888-01A1. Kenneth Blum served as Scientific Director of Path Foundation NY is the recipient of a grant from Life Extension Foundation, Ft. Lauderdale, Florida awarded to Path Foundation NY www.pathfoundationny.org. These funders provided support for authors [RDB, PT, KB], but did not have any additional role in the decision to publish, or preparation of the manuscript.

References

1. Bunzow JR, Van Tol HH, Grandy DK, Albert P, Salon J, Christie M, et al. Cloning and expression of a rat D2 dopamine receptor cDNA. Nature. 1988; 336: 783-787.
2. Wollemann M. Receptors acting through adenylate cyclase in the CNS. Acta physiologica Academiae Scientiarum Hungaricae. 1980; 55: 299-304.
3. Weiner DM, Brann MR. The distribution of a dopamine D2 receptor mRNA in rat brain. FEBS letters. 1989; 253: 207-213.
4. Grandy DK, Litt M, Allen L, Bunzow JR, Marchionni M, Makam H, et al. The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. Am J Hum Genet. 1989; 45: 778-785.
5. Volkow ND, Wiers CE, Shokri-Kojori E, Tomasi D, Wang GJ, Baler R. Neurochemical and metabolic effects of acute and chronic alcohol in the human brain: Studies with positron emission tomography. Neuropharmacology. 2017.
6. Dobbs LK, Lemos JC, Alvarez VA. Restructuring of basal ganglia circuitry and associated behaviors triggered by low striatal D2 receptor expression: implications for substance use disorders. Genes, brain and behavior. 2017; 16: 56-70.
7. Shumay E, Wiers CE, Shokri-Kojori E, Kim SW, Hodgkinson CA, Sun H, et al. New Repeat Polymorphism in the AKT1 Gene Predicts Striatal Dopamine D2/D3 Receptor Availability and Stimulant-Induced Dopamine Release in the Healthy Human Brain. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2017; 37: 4982-4991.
8. Blum K, Noble EP, Sheridan PJ, Finley O, Montgomery A, Ritchie T, et al. Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. Alcohol. 1991; 8: 409-416.
9. Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadeeswaran P, et al. Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA. 1990; 263: 2055-2060.
10. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Arch Gen Psychiatry. 1991; 48: 648-654.
11. Ding ZM, Ingraham CM, Rodd ZA, McBride WJ. The reinforcing effects of ethanol within the posterior ventral tegmental area depend on dopamine neurotransmission to forebrain cortico-limbic systems. Addiction biology. 2015; 20: 458-468.
12. Ding ZM, Katner SN, Rodd ZA, Truitt W, Hauser SR, Deehan GA, et al. Repeated exposure of the posterior ventral tegmental area to nicotine increases the sensitivity of local dopamine neurons to the stimulating effects of ethanol. Alcohol. 2012; 46: 217-223.

13. Levine A, Huang Y, Drisaldi B, Griffin EA, Pollak DD, Xu S, et al. Molecular mechanism for a gateway drug: epigenetic changes initiated by nicotine prime gene expression by cocaine. Science translational medicine. 2011; 3: 107-109.

14. Dyr W, McBride WJ, Lumeng L, Li TK, Murphy JM. Effects of D1 and D2 dopamine receptor agents on ethanol consumption in the high-alcohol-drinking (HAD) line of rats. Alcohol. 1993; 10: 207-212.

15. Mikhailova MA, Bass CE, Grinevich VP, Chappell AM, Deal AL, Bonin KD, et al. Optogenetically-induced tonic dopamine release from VTA-nucleus accumbens projections inhibits reward consummatory behaviors. Neuroscience. 2016; 333: 54-64.

16. Badgaiyan RD, Sinha S, Sajjad M, Wack DS. Attenuated Tonic and Enhanced Phasic Release of Dopamine in Attention Deficit Hyperactivity Disorder. PLoS One. 2015; 10: e0137326.

17. Buck K, Lischka T, Dorow J, Crabbe J. Mapping quantitative trait loci that regulate sensitivity and tolerance to quinpirole, a dopamine mimetic selective for D(2)/D(3) receptors. Am J Med Genet. 2000; 96: 696-705.

18. Noble EP. Alcoholism and the dopaminergic system: a review. Addict Biol. 1996; 1: 333-348.

19. Siciliano CA, Locke JL, Mathews TA, Lopez MF, Becker HC, Jones SR. Dopamine synthesis in alcohol drinking-prone and -resistant mouse strains. Alcohol. 2017; 58: 25-32.

20. Blum K, Elston SF, DeLallo L, Briggs AH, Wallace JE. Ethanol acceptance as a function of genotype amounts of brain [Met]enkephalin. Proc Natl Acad Sci U S A. 1983; 80: 6510-6512.

21. Blum K, Briggs AH, Elston SF, DeLallo L, Sheridan PJ, Sar M. Reduced leucine-enkephalin--like immunoreactive substance in hamster basal ganglia after long-term ethanol exposure. Science. 1982; 216: 1425-1427.

22. Xiao C, Ye JH. Ethanol dually modulates GABAergic synaptic transmission onto dopaminergic neurons in ventral tegmental area: role of mu-opioid receptors. Neuroscience. 2008; 153: 240-248.

23. Blum K, Sheridan PJ, Wood R, Braverman ER. Dopamine D2 receptor gene polymorphisms in Scandinavian chronic alcoholics: a reappraisal. Eur Arch Psychiatry Clin Neurosci. 1995; 245: 50-52.

24. Oberlin BG, Albrecht DS, Herring CM, Walters JW, Hile KL, Kareken DA, et al. Monetary discounting and ventral striatal dopamine receptor availability in nontreatment-seeking alcoholics and social drinkers. Psychopharmacology (Berl). 2015; 232: 2207-2216.

25. Febo M, Blum K, Badgaiyan RD, Baron D, Thanos PK, Colon-Perez LM, et al. Dopamine homeostasis: brain functional connectivity in reward deficiency syndrome. Front Biosci (Landmark Ed). 2017; 22: 669-691.

26. Blum K, Chen AL, Giordano J, Borsten J, Chen TJ, Hauser M, et al. The addictive brain: all roads lead to dopamine. J Psychoactive Drugs. 2012; 44: 134-143.

27. Oberlin BG, Dzemidzic M, Tran SM, Soeurt CM, Albrecht DS, Yoder KK, et al. Beer flavor provokes striatal dopamine release in male drinkers: mediation by family history of alcoholism. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2013; 38: 1617-1624.

28. Blum K, Trachtenberg MC, Elliott CE, Dingler ML, Sexton RL, Samuels AI, et al. Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and polydrug abusers: double-blind placebo-controlled study of the nutritional adjunct SAAVE. Alcohol. 1988; 5: 481-493.

29. Blum K, Trachtenberg MC, Ramsay JC. Improvement of inpatient treatment of the alcoholic as a function of neurotransmitter restoration: a pilot study. Int J Addict. 1988; 23: 991-998.

30. Brown RJ, Blum K, Trachtenberg MC. Neurodynamics of relapse prevention: a neuronutrient approach to outpatient DUI offenders. J Psychoactive Drugs. 1990; 22: 173-187.

31. Miller DK, Bowirrat A, Manka M, Miller M, Stokes S, Manka D, et al. Acute intravenous synaptamine complex variant KB220 “normalizes” neurological dysregulation in patients during protracted abstinence from alcohol and opiates as observed using quantitative electroencephalographic and genetic analysis for reward polymorphisms: part 1, pilot study with 2 case reports. Postgrad Med. 2010; 122: 188-213.

32. Chen TJ, Blum K, Payte JT, Schoolfield J, Hopper D, Stanford M, et al. Narcotic antagonists in drug dependence: pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy. Med Hypotheses. 2004; 63: 538-548.

33. Febo M, Blum K, Badgaiyan RD, Perez PD, Colon-Perez LM, Thanos PK, et al. Enhanced functional connectivity and volume between cognitive and reward centers of naive rodent brain produced by pro-dopaminergic agent KB220Z. PLoS One. 2017; 12: e0174774.

34. Dahlgren A, Wargelius HL, Berglund KJ, Fahlke C, Blennow K, Zetterberg H, et al. Do alcohol-dependent individuals with DRD2 A1 allele have an increased risk of relapse? A pilot study. Alcohol Alcohol. 2011; 46: 509-513.

35. Blum K, Chen TJ, Downs BW, Bowirrat A, Waite RL, Braverman ER, et al. Neurogenetics of dopaminergic receptor supersensitivity in activation of brain reward circuitry and relapse: proposing “deprivation-amplification relapse therapy” (DART). Postgrad Med. 2009; 121: 176-196.

36. Dani JA, De Biasi M. Mesolimbic dopamine and habenulo-interpeduncular pathways in nicotine withdrawal. Cold Spring Harb Perspect Med. 2013; 3.

37. Berggren U, Fahlke C, Berglund KJ, Wadell K, Zetterberg H, Blennow K, et al. Dopamine D2 receptor genotype is associated with increased mortality at a 10-year follow-up of alcohol-dependent individuals. Alcohol Alcohol. 2010; 45: 1-5.

38. Dackis CA, Gold MS. New concepts in cocaine addiction: the dopamine depletion hypothesis. Neuroscience and biobehavioral reviews. 1985; 9: 469-477.

39. Berman SM, Noble EP, Antolin T, Sheen C, Conner BT, Ritchie T. P300 development during adolescence: effects of DRD2 genotype. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology. 2006; 117: 649-659.

40. Blum K, Braverman ER, Dinardo MJ, Wood RC, Sheridan PJ. Prolonged P300 latency in a neuropsychiatric population with the D2 dopamine receptor A1 allele. Pharmacogenetics. 1994; 4: 313-322.

41. Hill SY, Locke J, Zezza N, Kaplan B, Neiswanger K, Steinhauer SR, et al. Genetic association between reduced P300 amplitude and the DRD2 dopamine receptor A1 allele in children at high risk for alcoholism. Biol Psychiatry. 1998; 43: 40-51.

42. Nacher V. Genetic association between the reduced amplitude of the P300 and the allele A1 of the gene which codifies the D2 dopamine receptor (DRD2) as possible biological markers for alcoholism. Revista de neurologia. 2000; 30: 756-763.

43. Lawford BR, Young RM, Noble EP, Sargent J, Rowell J, Shadforth S, et al. The D(2) dopamine receptor A(1) allele and opioid dependence: association with heroin use and response to methadone treatment. Am J Med Genet. 2000; 96: 592-598.