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Neurogenetics of Dopaminergic Receptor Super-sensitivity in Activation of Brain Reward Circuitry and Relapse: Proposing “Deprivation-Amplification Relapse Therapy” (DART)

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Abstract

Background and Hypothesis—It is well known that after prolonged abstinence, individuals who imbibe or use their drug of choice experience a powerful euphoria that precipitates serious relapse. While a biological explanation for this conundrum has remained elusive, we hypothesize that this clinically observed “super sensitivity” might be tied to genetic dopaminergic polymorphisms. Another therapeutic conundrum relates to the paradoxical finding that the dopaminergic agonist bromocriptine induces stronger activation of brain reward circuitry in individuals who carry the DRD₂ A1 allele compared to DRD₂ A2 allele carriers. Based upon the fact that carriers of the A1 allele relative to the A2 allele of the DRD₂ gene have significantly lower D₂ receptor density, a reduced sensitivity to dopamine agonist activity would be expected in the former. Thus, it is perplexing that with low D₂ density there is an increase in reward sensitivity with the dopamine agonist bromocriptine. Moreover, under chronic or long-term therapy, the potential proliferation of D₂ receptors with bromocriptine has been shown *in vitro*. This seems to lead to a positive outcome and significantly better treatment compliance only in A1 carriers.

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Competing interests

Kenneth Blum, Roger L. Waite, and William Downs, are Officers in LifeGen, Inc. San Diego, CA. LifeGen, Inc., which has the worldwide distribution rights of the Synaptamine Complex [KB220™]. There are no other conflicts of interest.

Authors' Contributions

KB- Investigator and major contributor to writing of manuscript and conception of theoretical concepts; **TJHC**- Co-investigator and contributor to hypotheses; **BWD**- Major editor and co-writer and conception of theoretical concepts; **AB**- co-investigator and major contributor to graphics; **RLW**- Contributor to clinical aspects and commentary; **ERB**- Co-writer and editorial support; **MOB**- Contributor to writing of the manuscript, editorial review, and comments; **ND**- Contributor to writing of the manuscript, editorial review and comments; **MSG**- Editorial review, co-writer of the manuscript, and contributor to the cited literature.

Proposal and Conclusion—We propose that low D₂ receptor density and polymorphisms of the D₂ gene are associated with risk for relapse of substance abuse including alcohol dependence, heroin craving, cocaine dependence, methamphetamine abuse, nicotine sensitization, and glucose craving. With this in mind, we suggest a putative physiological mechanism that may help to explain the enhanced sensitivity following intense acute dopaminergic D₂ receptor activation: “denervation supersensitivity.” Thus, the administration of dopamine D₂ agonists would target D₂ sensitization and attenuate relapse, especially in D₂ receptor A1 allele carriers. This hypothesized mechanism is supported by clinical trials utilizing the amino-acid neurotransmitter precursors, enkephalinase and catechol-O-methyl-transferase (COMT) enzyme inhibition, which have resulted in attenuated relapse rates in Reward Deficiency Syndrome (RDS) probands. Future warranted translational research with positive outcome showing prevented or lower relapse in RDS will ultimately support the proposed concept, which we term “Deprivation-Amplification Relapse Therapy (DART).”

Background

In 1996, our laboratory first described Reward Deficiency Syndrome (RDS) to define a common genetic variant involving dopamine D₂ receptor gene (DRD₂) polymorphisms [1–4] as a putative predictor of impulsive and addictive behaviors [5–7]. The D₂ receptor has been associated with pleasure, and the DRD₂ A1 allele has been referred to as a reward gene [8–10]. The DRD₂ gene has been one of the most widely studied in relation to neuropsychiatric disorders in general, and in alcoholism, other addictions, and related aberrant behaviors (e.g. carbohydrate craving), reward behaviors, and creativity in particular [11–19]. A recent PUBMED search resulted in 2,685 published reports on the subject. The Taq1 A1 allele, of this gene also may be involved in co-morbid antisocial personality disorder symptoms [20], high novelty seeking [21–23], and alcoholism [24]. Addiction is increasingly recognized to be one disease sharing a common neuroanatomy [25] and neurobiology [26]. The mesocorticolimbic dopaminergic pathway plays an especially important role in mediating the positive reinforcement of natural rewards like food and sex, as well as by drugs of abuse. As such, there may be a common neuronal circuitry for multiple addictions and for a number of psychiatric disorders [27–32].

When there is a dysfunction in the reactivity of the mesocorticolimbic dopamine reward system (potentially caused by certain genetic variants), the end result is Reward Deficiency Syndrome (RDS). RDS is a general condition or umbrella disorder [1, 2, 4, 33, 34], which tends to increase the risk for subsequent drug-seeking behavior [35, 36], as well as conditions such as ADHD, Tourette’s syndrome, and antisocial personality symptoms [5, 37, 46, 47]. RDS refers to the breakdown of a cascade of neurotransmitters in the brain in which one reaction triggers another – the reward cascade [48] — promoting intense cravings and resultant aberrant conduct, and it is tied to specific genetic and environmental influences [48]. It is well known that alcohol and other drugs of abuse [49], as well as most positive reinforcers (i.e. sex [50] food [51] gambling [52, 53], and in some cases aggression [6]), cause activation and neuronal release of brain dopamine [54, 55], which can decrease negative feelings and satisfy excessive desire for food, sex, and beverages [56–70]. A deficiency or absence of the D₂ receptors then predisposes individuals to a high risk for multiple addictive and impulsive behaviors [4, 70, 71].

Thus, low dopamine receptors may set up a physiological desire for dopamine and place an individual at high risk. Although other neurotransmitters (e.g. glutamate, gamma-aminobutyric acid (GABA) [72], serotonin [73], and enkephalins [74]) may be important in determining the rewarding and stimulating effects of substances such as ethanol, dopamine transporters may be critical for initiating drug use and for reinstating drug use during protracted abstinence [74–80].

Following the initial findings of a positive association of the Taq1 A1 of the DRD₂ gene and severe alcoholism, substance dependence, and related behaviors [16], there have been many replication studies (including linkage to ANKK1 gene and other markers) [14, 16, 18, 20, 23, 24, 32, 56, 62, 76, 79, 81–106] as well as some that have failed to find this relationship [107–119] (see reviews) [4, 24, 71, 72, 120–135].

It has been observed that the Taq1 A1 allele is associated with low dopamine D₂ receptor density in alcoholics [87]. Moreover, other studies have confirmed that the striatal post-synaptic D₂ receptor densities are low among alcoholics [136]. The dopamine transporter system is involved in clearing dopamine from the synapse affecting reward sensitivity, and studies of pre- and post-synaptic D₂ receptors, as well as dopamine transporter (DAT) densities among late-onset (Type I) and violent (Type II) alcoholics, have suggested an underlying dopaminergic defect [137–141]. High DAT densities among violent Type II alcoholics were reported when compared with healthy controls [139], while late-onset Type I alcoholics had lower densities than healthy controls [137]. Another study using the highly selective radioligand PE2I technique [140] reported lower DAT densities among alcoholics compared with controls, but subtypes were not considered [89].

Even in the first paper by Blum *et al* in 1990 [16], the concept of the dopamine D₂ receptor gene as a specific target for alcohol was appropriately dismissed by the authors, who suggested that they have found a non-specific “reward” gene. Moreover, the DRD₂ Taq1 A allele as well as the 957C>T polymorphism have been also associated with sensitivity to stress and anxiety [82, 142–146], and both symptoms have been related to sensitivity of pre-synaptic D₂ receptors [9, 147]. The sensitivity is elevated in high anxiety subjects compared with low anxiety subjects. Furthermore, other RDS and related neurological and psychiatric disorders are also found to be associated with polymorphisms of the DRD₂ gene.

Hypothesis

Grasping the mechanism of motivated behavior requires an understanding of the neural circuitry of rewards [154], otherwise called positive reinforcers. A positive reinforcer is operationally defined as an event that increases the probability of a subsequent response, and drugs of abuse are considered to be stronger positive reinforcers than natural reinforcers (e.g. food and sex) [155–157]. The distinction between “natural rewards” and “unnatural rewards” is an important one. Natural rewards include satisfaction of physiological drives (e.g. hunger and reproduction), and unnatural rewards are learned and involve satisfaction of acquired pleasures such as hedonic sensations [158] derived from alcohol and other drugs, as well as from gambling and other risk-taking behaviors [155, 159, 160]. In discussing RDS, we refer specifically to an insensitivity and inefficiency in the acquired (or unnatural) reward system [1–4] and this breakdown of the reward system in genetically prone individuals may lead to the acquiring of unnatural rewards. RDS also encompasses the acquired need to escape or avoid negative effects created by repeated cycles of alcohol and drug abuse [161] or repetitive bouts of overeating [162].

Dopamine has been associated with pleasure, and it has been called the “anti-stress molecule” and/or the “pleasure molecule” mediating non-drug behaviors such as sex and gambling [2, 82, 163, 164, 165]. When dopamine is released into the synapse, it stimulates a number of receptors (D₁–D₅) which results in increased feelings of wellbeing and stress reduction. The neural circuitry for positive reinforcement involves multiple brain regions. Core regions constituting the brain reward pathway are located in the limbic system [72]. Importantly, the DRD₂ Taq1A polymorphism is associated with dopamine D₂ receptor density, which plays an important role in the context of reward. As cited above, persons carrying an A1 allele have a lower D₂ receptor density and a higher risk of substance abuse.

One study was designed to investigate the influence of the DRD₂ TaqIA polymorphism and the selective D₂ receptor agonist bromocriptine on the activation of the reward system by means of functional magnetic resonance imaging (fMRI). In a double-blind crossover study with 24 participants Kirsch *et al* [166] found an increase of reward system activation from placebo to bromocriptine only in subjects carrying the A1 allele. Furthermore, only A1 carrier showed an increase of performance under bromocriptine. The results are interpreted as reflecting a specific sensitivity for dopamine agonists in persons carrying an A1 allele and may complement actual data and theories of the development of addiction disorders postulating a higher genetic risk for substance abuse in carrier of the A1 allele [92].

This finding at first glance seems paradoxical due to having low dopamine D₂ receptors in DRD₂ A1 allele carriers compared to DRD₂ A2 carriers. Especially, when one considers the more intuitive potential of blunted brain dopaminergic response to a palatable sugar. [51]. However, we are proposing “Denervation Supersensitivity” phenomena as a reasonable resolution of this paradox (see Figures 1–3).

Denervation Supersensitivity: Supporting evidence for “Deprivation-Amplification Relapse Therapy” (DART)

We propose the use of Deprivation-Amplification Relapse Therapy (DART) as a novel adjunct in the treatment of addictive disorders. DART also illuminates a solution to a longstanding clinical conundrum, whereby after a prolonged abstinence the consumption or use of an individual’s drug of choice induces a powerful euphoria that precipitates serious relapse. If the ideas proposed herein are confirmed, DART could become a putative modality to prevent relapse, especially in D₂ deficient genetic carriers of DRD₂ A1 allele.

The process of receptor supersensitivity has a long history and is an epiphenomenon of neuronal denervation. Dopamine receptor supersensitivity similarly occurs after dopamine denervation, and this process is invoked in neuropsychiatric and neurodegenerative disorders. From studies largely over the past 25 years, much has been learned regarding dopamine receptor supersensitivity. For example, overt D₁ dopamine receptor supersensitivity occurs after perinatal destruction of nigrostriatal dopamine fibers. However, following perinatal destruction of dopamine innervation, the most-prominent behavioral effects of a D₁ agonist are observed after a series of D₁ agonist treatments—a process known as priming of D₁ dopamine receptors. Moreover, perinatal lesioning of dopamine fibers produces prominent serotonin (5-HT) receptor supersensitivity, and in fact 5-HT receptor supersensitivity appears to modulate D₁ dopamine receptor supersensitivity. In rodents, receptor supersensitization by these means appears to be irreversible. In contrast to the observed D₁ dopamine receptor supersensitivity, D₂ dopamine receptor supersensitivity apparently does not occur after perinatal dopamine denervation. Also, while repeated D₁ agonist treatment of intact rats has no observable effect, repeated D₂ agonist treatments, during or after the ontogenetic phase, produces prominent life-long D₂ receptor supersensitivity. The process may have an association with substance abuse. Therefore, production of D₁ and D₂ dopamine receptor supersensitivity occurs by different means and under different circumstances, and in association with perhaps different neuronal phenotypes, and with greater incidence in either intact (D₂) or dopamine-lesioned counterparts (D₁). The physiological consequences of receptor supersensitivity are multiple [167]. In this regard, we are also proposing that D₂ receptor supersensitivity occurs in DRD₂ A1 allele carriers at birth thus the infant and ultimately the growing adolescent is at high risk for Substance Use Disorder (a clinical subtype of RDS).

One example of this concept comes from earlier work [168]. Previous studies have suggested that postjunctional supersensitivity of the vas deferens is due in part to altered

electrophysiological properties, the sensitivity of the muscle being increased to any agonist which initiates contraction by means of depolarizing the cell membrane. Work from the laboratory of Westfall [168] indicates that altered electrical properties are not the only postjunctional changes, which can account for the enhanced response. Dose-response curves for stimulant agonists were obtained in isolated *vasa deferentia* which were depolarized by a K-rich, Na-free solution. Chronic denervation resulted in a 2- to 3-fold displacement of the dose-response curve for norepinephrine to the left of control. Cocaine (10⁻⁵ M) did not potentiate the response to norepinephrine of the innervated, depolarized smooth muscle. Supporting the contention that the supersensitivity of the depolarized tissue is postjunctional in nature was the finding that the denervated vas deferens was supersensitive to methoxamine, an agent which is not taken up by the neuronal amine transport system. Pretreatment of rats with reserpine (1.0 mg/kg/day for 5–7 days) [reducing the neurotransmitter norepinephrine] also produced supersensitivity of the depolarized vas deferens. Thus lower postjunctional sites as a result of neurotransmitter depletion caused by either denervation or reserpine leads to an adaptive supersensitivity of any agonist. This phenomenon has been confirmed by a series of experiments reported by Blum's group [169–171] also involving vas deferens and supersensitivity to norepinephrine following ethanol and cannabis in utero. Therefore it is feasible that when there is a low density [A1 carriers] of postjunctional D₂ receptors compared to a higher “normal” compliment of D₂ receptors (A2 carriers) [just like denervation] powerful D₂ agonists like bromocriptine, unlike weak non-specific dopamine releasers like glucose (binding to five dopamine receptors) induces a “supersensitive” higher activation of the reward circuitry instead of an expected blunted response. These phenomena may have important therapeutic implications especially in relapse prevention.

Relapse as a Function of Dopamine Sensitization: Genetic Antecedents and Attempts at a Systems Approach toward Understanding Underlying Brain Mechanisms

“Systems Biology” and the genomics thereof may provide a model for understanding the underlying pathophysiology of substance abuse and craving. Knowledge based upon the interactions among various environmental and genetic factors will ultimately be helpful for successful treatment and relapse prevention.

Drug addiction is characterized by motivational disturbances such as compulsive drug taking and episodes of intense drug craving. Recent advances using animal models of relapse have shown that drug-seeking behavior can be triggered by drug-associated cues, by stress, and by priming injections of the drugs themselves, events also known to trigger drug craving in human drug addicts. Current evidence suggests that these stimuli all induce relapse, at least in part, by their common ability to activate the mesolimbic dopamine system. Drug-associated cues and stress can activate this system *via* neural circuits from the prefrontal cortex and amygdala and through activation of the hypothalamic-pituitary-adrenal axis.

Studies by Self [172] have suggested that dopamine triggers relapse to drug-seeking behavior by stimulating D₂-dopamine receptors which inhibit the cyclic AMP second messenger pathway in the neurons of the nucleus accumbens. In contrast, compounds that activate D₁ receptors prevent relapse to drug-seeking behavior, possibly through satiation of reward pathways. Chronic neuro-adaptations in dopamine receptor signaling pathways in the nucleus accumbens caused by repeated drug use are hypothesized to produce tolerance to the rewarding effects of D₁-receptor stimulation, leading to increased drug intake during drug self-administration. Conversely, these same neuro-adaptations are hypothesized to enhance drug craving by potentiating D₂ receptor-mediated signals during abstinence. These findings

identify D₁ and D₂-dopamine receptor mechanisms as potential targets for developing anti-craving compounds to treat drug addiction. It is further postulated by us that the sensitization of dopamine during abstinence may occur when the D₂ receptors are compromised as in the case of DRD₂ A1 allele carriers [173]. This notion is supported in part by the work of Li *et al* [174]. Subjective craving is considered to be a central phenomenon, which contributes to the continuation of drug use in active abuser and the occurrence of relapse in detoxified abusers. The Dopaminergic pathway has been implicated in the cue-elicited craving for a variety of addictive substances. The objective of the Li [174] study was to test the hypothesis that heroin addicts carrying specific variants in dopamine-related genes would have higher levels of craving following exposure to a heroin-related cue. Craving induced by a series of exposure to heroin-related cue was assessed in a cohort of Chinese heroin abuser (n = 420) recruited from natural abstinence center at Shanghai. Significantly stronger cue-elicited heroin craving was found in individuals carrying D₂ dopamine receptor gene (DRD₂) TaqI RFLP A1 allele than the non-carriers ($p < 0.001$). Furthermore, they did not observe significant association of cue-elicited craving with the nine-repeat allelic variants in dopamine transporter gene (DAT) SLC6A3 and with the dinucleotide repeat polymorphism (DRP) 148bp allele in D5 dopamine receptor gene (DRD5). The results of their study suggest that human dopaminergic pathways, especially in D₂ A1 allele carriers, are involved in cue-induced heroin craving, and indicate a potential genetic risk factor for persistent heroin abuse as well as relapse. Furthermore this phenomena was not specific to just heroin, Ujike [175] also found that as to risks of rapid onset of methamphetamine psychosis, worse prognosis or complication of spontaneous relapse, the dopamine D₂ receptors, monoamine oxidase-A, catechol-O-methyltransferase, among other related genes were identified. In addition, Perkins *et al* [176] found similar evidence for both the DRD₂ and OPRM1 genes and nicotine. (smoking behavior). They found an increase in smoking amount owing to negative mood was associated with: dopamine D₂ receptor (DRD₂) C957T (CC>TT or CT), SLC6A3 (presence of 9 repeat>absence of 9), and among those given a nicotine cigarette, DRD4 (presence of 7 repeat>absence of 7) and DRD₂/ANKK1 TaqI A (TT or CT>CC). SLC6A3, and DRD₂/ANKK1 TaqIA were also associated with smoking reward and smoking latency. OPRM1 (AA>AG or GG) was associated with smoking reward, but SLC6A4 variable number tandem repeat was unrelated to any of these measures.

The specific role of the D₂ receptors and glutamate receptors in cocaine relapse has been recently explored by Bachtell *et al* [177] in an elegant gene therapy study. It is well known that chronic cocaine use reduces glutamate levels in the nucleus accumbens (NAc), and is associated with experience-dependent changes in (+/-)-alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptor membrane expression in NAc neurons. These changes accompany behavioral sensitization to cocaine and increased susceptibility to cocaine relapse. The functional relationship between neuroplasticity in AMPA receptors and the behavioral manifestation of cocaine addiction remains unclear. Bachtell *et al* [177] examined the behavioral effects of up- and down-regulating basal AMPA receptor function in the NAc core and shell using viral-mediated gene transfer of wild-type glutamate receptor 1 (wt-GluR1) or a dominant-negative pore-dead GluR1 (pd-GluR1), respectively. Transient increases in wt-GluR1 during or after cocaine treatments diminished the development of cocaine sensitization, while pd-GluR1 expression exacerbated cocaine sensitization. Parallel changes were found in D₂ but not D₁ receptor-mediated behavioral responses. As a correlate of the sensitization experiments, the researchers over-expressed wt- or pd-GluR1 in the NAc core during cocaine self-administration, and tested the effects on subsequent drug-seeking behavior three weeks after over-expression declined. wt-GluR1 over-expression during self-administration had no effect on cocaine intake, but subsequently reduced cocaine seeking in extinction and cocaine-induced reinstatement, whereas pd-GluR1 facilitated cocaine-induced reinstatement. When over-expressed during reinstatement tests, wt-GluR1 directly attenuated cocaine- and

D₂ agonist-induced reinstatement, while pd-GluR1 enhanced reinstatement. In both experimental procedures, neither wt- nor pd-GluR1 expression affected cue-induced reinstatement. Together, these results suggest that degrading basal AMPA receptor function in NAc neurons is sufficient to facilitate relapse *via* sensitization in D₂ receptor responses, whereas elevating basal AMPA receptor function attenuates these behaviors. Finally dopamine sensitization D₂ genetics has been associated with severe alcohol relapse behavior as well [178].

“Deprivation-Amplification Relapse Therapy” [DART]

As we discussed earlier, relapse of psychoactive drugs may be due to specific genetic polymorphic antecedents. However, since stress by itself is a very important environmental element in terms of inducing relapse, the next section will focus on neuropsychogenetics of this environmental influence.

Underlying psychiatric mechanisms of stress

Stressful situations will stimulate dopamine transmission in both the medial prefrontal cortex and the NAc in the meso-limbic part of the brain (“reptilian brain”) [179]. It appears, however, that the NAc dopamine response to stressful conditions is modulated by a dopamine-sensitive mechanism in prefrontal cortex such that increased dopamine transmission in this cortical region acts to dampen the NAc dopamine response to a variety of stimuli including those that induce stress [179, 180–181]. There is evidence implicating also prefrontal cortex glutamate- (GLUT-) containing neurons some of which are known to project to NAc and to the ventral tegmental area (VTA) where the mesocorticolimbic dopamine system originates [182–184].

In addition to stimulating dopamine transmission, stress will also increase prefrontal cortex and NAc levels of GLUT [185] and there is evidence indicating that the NAc dopamine response to stress is modulated locally by a GLUT-sensitive mechanism [186–189]. It has been reported that the NAc dopamine stress response is potentiated by local NMDA receptor blockade [190]. In that study the researchers reported evidence that the local action of GLUT on the NAc dopamine stress response is mediated by NMDA receptors located on NAc output neurons that project to the VTA. Part of this output system comprises GABA neurons that project to the VTA either directly or indirectly *via* the ventral pallidum [191–193]. In the VTA, GABA is known to hyperpolarize dopamine cells, inhibiting their activity by a direct GABA_B receptor-mediated action [194, 195]. The activity of VTA dopamine cells is also regulated by GABA acting at GABA_A receptors although here the evidence indicates both a direct inhibitory action as well as a predominant indirect disinhibitory action presumably mediated presynaptically by GABA_A receptors on non-dopamine interneurons [196–202]. Local VTA GABA_A and GABA_B receptor activation has been shown previously to modulate dopamine transmission in NAc and VTA. However, to our knowledge, similar information has not been obtained for the NAc dopamine response to stress.

Recent results indicate that the NAc dopamine stress response is regulated by GABA afferents to VTA dopamine cells and that this action is differentially mediated by GABA_A and GABA_B receptors. The data suggest that the relevant GABA_B receptors are located on dopamine neurons, whereas the GABA_A receptors are located on GABA inter-neurons and perhaps also on dopamine cells.

The finding related to stress reduction by Synapatamine™ in polysubstance abusers as seen in a recent study from our laboratory [203] is consistent with the idea that the corticofugal GLUT input to NAc indirectly regulates stress-induced dopamine release in this region through the GABA feedback pathway to VTA.

Moreover, in the past decade, it has also become clear that vulnerability for substance use disorders is influenced by complex interactions between genetic and environmental determinants [204–209]. Interestingly, impulsive behaviors often increase under conditions of heightened arousal or stress [204]. Associations between stress and substance abuse have also been well documented [210–214]. Recent preclinical findings suggest that the dopamine system may be an important vulnerability substrate in this relation [215–218]. Nevertheless, the exact nature of stress-induced alterations on dopamine neurotransmission, the conditions under which these alterations occur, and the ability to generalize the preclinical findings to humans, remain to be determined [219].

Since the findings of Blum *et al* [16] associating the dopamine D₂ receptor gene polymorphisms and severe alcoholism, many studies have also associated a number of DRD₂ gene polymorphisms with various forms of stress both acute and chronic [144

In the recent double-blinded placebo controlled randomized study of patients in an inpatient treatment facility, Blum *et al* [203] analyzed the stress relieving effects of Synaptamine Complex™ [KB220] (LifeGen, Inc., San Diego, CA), a novel nutraceutical with putative dopaminergic activation properties. This nutraceutical was designed to mimic the natural release of VTA dopamine from the NAc, resulting in a reduction of substance seeking behavior based on dopaminergic genetics [220–223].

Dopamine and the D₂ receptor gene has been correlated with susceptibility to depressive symptoms during stressful life events and results support a role for DRD₂ as a susceptibility gene for alcohol dependence within multiplex families at high risk for developing alcohol dependence [224], more severe stress or stress disorders [209, 225]. Moreover, our research and that of others throughout the years have provided evidence that pharmacogenetic and/or nutrigenetic testing prior to administration of any agent to treat psychiatric based disorders should significantly improve treatment outcomes [91, 226].

In fact as mentioned earlier, Kirsch *et al* [166] in a double-blind crossover study with 24 participants found an increase of reward system activation from placebo to bromocriptine only in subjects carrying the A1 allele. This work supports the work of Noble's group [91]. Furthermore, only A1 carrier showed an increase of performance under bromocriptine. The results are interpreted as reflecting a specific sensitivity for dopamine agonists in persons carrying an A1 allele and may complement actual data and theories of the development of addiction disorders postulating a higher genetic risk for substance abuse and proneness to stress in carriers of the A1 allele. This work is in agreement with earlier research from our laboratory [226, 227].

Finally, stress is a well-known risk factor in the development of addiction and in addiction relapse vulnerability. A series of population-based and epidemiological studies have identified specific stressors and individual-level variables that are predictive of substance use and abuse. Preclinical research also shows that stress exposure enhances drug self-administration and reinstates drug seeking in drug-experienced animals.

The deleterious effects of early life stress, child maltreatment, and accumulated adversity on alterations in the corticotropin releasing factor and hypothalamic-pituitary-adrenal axis (CRF/HPA), the extrahypothalamic CRF, the autonomic arousal, and the central noradrenergic systems are considered important. Noradrenergic activation is tantamount to ones extent of the severity of stressful events [209, 225]. The effects of these alterations on the corticostriatal-limbic motivational, learning, and adaptation systems that include mesolimbic dopamine, glutamate, and GABA pathways are all associated with the underlying pathophysiology linked with stress-related risk of addiction [228].

Furthermore, the CRF-like peptides, which include the mammalian peptides CRF, urocortin 1, urocortin 2, and urocortin 3, play an important role in orchestrating behavioral and physiological responses that may increase an organism's chance of survival when confronted with internal or external stressors. There is, however, evidence that a chronic over activity of brain CRF systems under basal conditions may play a role in the etiology and maintenance of psychiatric disorders such as depression and anxiety disorders. Bruijnzeel and Gold [229] suggest evidence of a role for CRF-like peptides in acute and protracted drug abstinence syndromes and relapse to drug-taking behavior. They suggest that there is a high co-morbidity between stress-associated psychiatric disorders and drug dependence.

Interestingly, in one study, stress was assessed in 36 inpatient treatment-engaged cocaine dependent individuals and 36 demographically matched healthy control participants using the Perceived Stress Scale and repeated morning salivary cortisol levels over three consecutive days. The Rey Auditory Verbal Learning Test was conducted to measure verbal learning, memory, and executive function. Prospective assessment of cocaine use outcomes during 90 days following discharge from inpatient treatment was also conducted. Fox *et al* [230] found that cocaine dependent patients showed higher levels of distress compared to controls in Perceived Stress Scale scores and cortisol levels. They also demonstrated a significantly reduced learning curve, and fewer correct responses and more errors on recognition. Elevated cortisol was significantly associated with worse Rey Auditory Verbal Learning test performance in cocaine dependent patients. Poor memory scores, but not distress measures, were significantly associated with greater cocaine use after inpatient treatment. The authors suggest that their findings are the first to demonstrate that learning and memory deficits in cocaine dependent individuals are associated with enhanced cortisol and with cocaine use outcomes after inpatient treatment. The findings are consistent with recent addiction models suggesting that chronic cocaine-related neuroadaptations affect learning and memory function, which in turn, influence drug use outcomes.

Moreover, relapse to drug taking induced by exposure to cues associated with drugs of abuse is a major challenge to the treatment of drug addiction. Previous studies indicate that drug seeking can be inhibited by disrupting the reconsolidation of a drug-related memory. Stress plays an important role in modulating different stages of memory including reconsolidation. Wang *et al* [231] determined the role of glucocorticoid receptors in the basolateral amygdala (BLA) in modulating the effects of stress on reconsolidation of this memory. The disruptive effect of stress on reconsolidation of morphine related memory was prevented by inhibition of corticosterone synthesis with metyrapone or basolateral amygdala, but not central amygdala, injections of the glucocorticoid antagonist RU38486 [(11,17)-11-[4-(dimethylamino) phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one]. Finally, the effect of stress on drug related memory reconsolidation was mimicked by systemic injections of corticosterone or injections of RU28362 [11,17-dihydroxy-6-methyl-17-(1-propynyl)androsta-1,4,6-triene-3-one] (a glucocorticoid receptor agonist) into basolateral amygdala, but not the central amygdala. These results show that stress blocks reconsolidation of a drug-related memory, and this effect is mediated by activation of glucocorticoid receptors in the basolateral amygdala. These findings may have important clinical implications especially in in-patients undergoing treatment. In fact, it may have profound influence on the well-known treatment phenomena called AMA rate (Withdrawal Against Medical Advice). It is of note that stress may induce AMA rates by virtue of disrupting reconciliation of drug-related memory. In other studies our laboratory has shown the significant decrease in AMA rate in "in-patient" cocaine dependent patients administered a Synaptamine™ variant (KB220) [232, 233]. Thus, one proposed mechanism is that KB220 prevented AMA rate because of its putative anti-stress property, thereby allowing for normalized reconciliation drug-related memory to occur.

Stress associated effects with dopamine D₂ receptor polymorphisms have been intensely studied. Gilbert *et al* [234] found that Nicotine Replacement Therapy reduced personality traits related to negative affect. Negative affect was found to a greater extent in DRD₂ A1 carriers than in A2A2 individuals during the first two weeks of treatment (when on the 21-mg patch); however, A1 carriers experienced a renewal of negative affect symptoms when switched to the 7-mg patch and when off the patch, while A2A2 individuals continued to benefit from nicotine replacement therapy. Other work by Coming's group [209] found a significant interaction between DRD₂ genotype and stress score as a predictor of MAST score in alcoholics. Additionally, this difference was found to be largely accounted by the HSI occupational/economic stress score, which interacted significantly with DRD₂ genotype as a predictor of MAST score. This stress score was the only one of four that showed levels of stress as high as HSI scores in a US population. The MAST scores of A2A2 genotype participants were found to be nearly identical in low stress and high stress participants, whereas the MAST scores of A1A2 participants increased modestly with stress, and that of A1A1 participants increased markedly with stress. Accordingly, these findings support the hypothesis that DRD₂ genotype-phenotype associations depend on the magnitude of stress exposure, and they lend support to the view that variability in DRD₂ study outcomes may in part be explained by this gene-environment interaction (see Figure 4).

In a recent paper, Koob [235] has suggested the following:

“Drug addiction can be defined by a compulsion to seek and take drug, loss of control in limiting intake, and the emergence of a negative emotional state when access to the drug is prevented. Drug addiction impacts multiple motivational mechanisms and can be conceptualized as a disorder that progresses from impulsivity (positive reinforcement) to compulsivity (negative reinforcement). The construct of negative reinforcement is defined as drug taking that alleviates a negative emotional state. The negative emotional state that drives such negative reinforcement is hypothesized to derive from dysregulation of key neurochemical elements involved in reward and stress within the basal forebrain structures involving the ventral striatum and extended amygdala. Specific neurochemical elements in these structures include not only decreases in reward neurotransmission, such as decreases in dopamine and opioid peptide function in the ventral striatum, but also recruitment of brain stress systems, such as CRF, in the extended amygdala. Acute withdrawal from all major drugs of abuse produces increases in reward thresholds, increases in anxiety-like responses, and increases in extracellular levels of CRF in the central nucleus of the amygdala. CRF receptor antagonists also block excessive drug intake produced by dependence. A brain stress response system is hypothesized to be activated by acute excessive drug intake, to be sensitized during repeated withdrawal, to persist into protracted abstinence, and to contribute to the compulsivity of addiction. Other components of brain stress systems in the extended amygdala that interact with CRF and may contribute to the negative motivational state of withdrawal include norepinephrine, dynorphin, and neuropeptide Y. The combination of loss of reward function and recruitment of brain stress systems provides a powerful neurochemical basis for a negative emotional state that is responsible for the negative reinforcement driving, at least in part, the compulsivity of addiction.” (p. S18)

Moreover, norepinephrine is considered the stress molecule, and dopamine is considered the anti-stress molecule. In fact, therapies that block norepinephrine function have been proposed as a treatment for psychoactive stimulant abuse [236]

Moreover, research on drug abuse has recently focused on understanding the vulnerability to develop addiction that is present in certain individuals. These investigations suggest that addiction results from an interaction between drugs and specific individual substrates. Differences in the propensity to develop drug intake can be demonstrated in animals with

equal access to drugs under stable laboratory conditions and can be predicted by drug-independent behaviors. Stress, corticosterone, and mesencephalic dopaminergic neurons seem to be organized in a pathophysiological chain which determines one's vulnerability. An increased corticosterone secretion, or a higher sensitivity to the effects of this hormone, either naturally present in certain individuals or induced by stress in others, increases the vulnerability to develop drug intake, *via* an enhancement of the activity of mesencephalic dopaminergic neurons. These findings suggest that addiction therapies should counteract the biological peculiarity that leads some individuals to respond in a pathophysiological way to drugs.

Specific targeting of dopaminergic sensitization by administering D₂ agonists in a slow, continual, non-powerful manner should result in an enhanced D₂ proliferation even in DRD₂ A1 probands.

In one supportive example, although bupropion and nicotine replacement therapy are efficacious tobacco dependence treatments, there is substantial inter-individual variability in therapeutic response, and most smokers relapse. Pharmacogenetics research may improve treatment outcomes by identifying genetic variants predictive of therapeutic response. Lerman *et al* [237] investigated the roles of two functional genetic variants in the dopamine D₂ receptor (DRD₂) gene in response to pharmacotherapy for tobacco dependence among participants in two randomized clinical trials with a 6-month follow-up period: a double-blind placebo-controlled trial of bupropion (n=414) and an open label trial of transdermal nicotine *vs.* nicotine nasal spray (n=368). At the end of the treatment phase, a statistically significant ($p=0.01$) interaction between the DRD₂ - 141C Ins/Del genotype and treatment indicated a more favorable response to bupropion among smokers homozygous for the Ins C allele compared to those carrying a Del C allele. By contrast, smokers carrying the Del C allele had statistically significantly ($p=0.006$) higher quit rates on nicotine replacement therapy compared to those homozygous for the Ins C allele, independent of type of nicotine replacement therapy. The C957T variant was also associated ($p=0.03$) with abstinence following nicotine replacement therapy. These results suggest that bupropion may be the preferred pharmacologic treatment for smokers homozygous for the DRD₂ - 141 Ins C allele, while nicotine replacement therapy may be more beneficial for those who carry the Del C allele. These results once again support the role of the DRD₂ gene and certain polymorphisms further support of the role of this gene and relapse risk as well as therapeutic support of DART.

It is noteworthy that preliminary research with Synaptamine™ variants [KB220] (a putative D₂ receptor agonist) by Blum's group have shown reduced relapse rates compared to standardized traditional treatment in two out-patient studies. In one study by Brown *et al* [238] driving-under-the-influence (DUI) offenders with either alcohol- or cocaine-related problems were studied. The neuronutrients SAAVE and Tropamine [both Synaptamine variants] significantly reduced relapse rates and enhanced recovery in these DUI outpatient offenders over a 10-week period. Follow-up on both the SAAVE and Tropamine groups after 10 months revealed a 73% and a 53% overall recovery rate, respectively.

In a second out-patient study by Chen *et al* [239] 76 patients (45 males and 31 females; mean age, 33 y [standard deviation, 7.0] who had been given a diagnosis of serious substance use disorder were recruited. After exclusion of 15 patients who dropped out before the end of the study, self-reported craving decreased from program entrance to 12 wk (visual analog scale whereby 0 represents no craving and 5, the strongest craving) for 61 compliant patients (mean decrease, 2.85, 95% confidence interval [CI], 2.65, 3.05); this improvement was significant ($p<.001$). Building up to relapse scores (each of 5 individual items and summary value) showed similar improvement after 1 y of treatment; the mean

decrease in scores was significant for stress ($t=3.3$; $p=.002$), depression ($t=4.0$; $p<.001$), anger ($t=4.4$; $p<.001$), anxiety ($t=4.5$; $p<.001$), drug craving ($t=5.4$; $p<.001$), and summary building up to relapse ($t=4.1$; $p<.001$). Also, recovery score measures of energy level ($t=8.4$; $p<.001$) and ability to refrain from drug-seeking behavior ($t=7.4$; $p<.001$) showed significant mean increases from entry to 1 y. During the study, the alcoholic dropout rate was only 7% (4 of 57), and the opiate abuses had a drop-out rate of 0%. A summary of combining this data suggests that utilization of a putative D₂ agonist could ultimately lead to a significant reduction of relapse rates of only 20.25% [see Table 1]. Other studies also utilizing Synaptamine variants result in positive anti-drug seeking behavior in both in-patient [240] and out-patient [241] treatment.

Conclusions

Individuals who re-imbibe their drug of choice, subsequent to a long period of abstinence, experience a powerful euphoria that precipitates serious relapse. Additionally, the dopaminergic agonist bromocriptine induces stronger activation of brain reward circuitry in individuals who carry the DRD2 A1 allele compared to DRD2 A2 allele carriers. We hypothesize that this clinically observed “super sensitivity” may be tied to genetic dopaminergic polymorphisms. Based upon the fact that carriers of the A1 allele relative to the A2 allele of the DRD2 gene have significantly lower D₂ receptor density, a reduced sensitivity to dopamine agonist activity would be expected in the former. Thus, it is perplexing that with low D₂ density there is an increase in reward sensitivity with the dopamine agonist bromocriptine. Moreover, under chronic or long-term therapy, the potential proliferation of D₂ receptors with bromocriptine has been shown *in vitro*. This seems to lead to a positive outcome and significantly better treatment compliance only in A1 carriers.

We have proposed that low D₂ receptor density and polymorphisms of the D₂ gene are associated with risk for relapse of substance abuse including alcohol dependence, heroin craving, cocaine dependence, methamphetamine abuse, nicotine sensitization, and glucose craving. With this in mind, we suggest a putative physiological mechanism that may help to explain the enhanced sensitivity following intense acute dopaminergic D₂ receptor activation: “denervation supersensitivity.” Thus, the administration of dopamine D₂ agonists would target D₂ sensitization and attenuate relapse, especially in D₂ receptor A1 allele carriers. This hypothesized mechanism is supported by clinical trials utilizing the amino-acid neurotransmitter precursors, enkephalinase and catechol-O-methyl-transferase (COMT) enzyme inhibition, which have resulted in attenuated relapse rates in Reward Deficiency Syndrome (RDS) probands. Future warranted translational research with positive outcome showing prevented or lower relapse in RDS will ultimately support the proposed concept, which we term “Deprivation-Amplification Relapse Therapy (DART).”

It is of interest that carriers of the DRD₂ A1 allele compared to DRD₂ A2 have a blunted response to putatively less powerful neuronal dopamine releasers such as glucose and monetary rewards and this may provide the incentive of a continual need for either palatable foods or gaming [245] as part of a “wanting” mechanism [51, 246]. As already stated this is opposite of an amplified activation of reward circuitry with powerful D₂ agonists like bromocriptine. [166]. The continued utilization of bromocriptine leads to a down-regulation of D₂ receptors *in vivo* [247] only in non-lesioned striata but not *in vitro* [243, 244]. To prevent relapse intrusively the best approach would be to reduce dopamine “supersensitivity” (i.e. craving behavior) by providing a D₂ agonist that will have the characteristic of up-regulation rather than down-regulation of D₂ receptors. However, this differential acute amplification effect will remain a puzzle until more research using both fMRI and PET scans are performed.

As an anti-relapse compound for incorporation into a treatment regimen, we propose a slow natural physiologically active D₂ agonist (e.g. Synaptamine Complex [KB220]TM), because it should increase D₂ receptors. It a preferred approach compared to a more powerful D₂ pharmacologically active compound (e.g. bromocriptine), which may cause a down regulation of D₂ receptors following continual activation [247]. The role of dopamine has been adequately studied in protracted abstinence, and findings of Volkow *et al* [248] are in agreement with our conceptualization of D₂ agonist therapy.

This concept in support of DART includes but is not limited to studies involving ADHD as well smoking behavior as examples of the mechanisms to support this novel therapeutic proposal. The mechanisms underlying the effects of psychostimulants in attention deficit hyperactivity disorder (ADHD) are not well understood, but indirect evidence implicates D₂ dopamine receptors. Fan and Hess [249] dissect the components of dopaminergic neurotransmission in the hyperactive mouse mutant coloboma to identify pre- and postsynaptic elements essential for the effects of amphetamine in these mice. Amphetamine treatment reduced locomotor activity in coloboma mice, but induced a robust increase in dopamine overflow suggesting that abnormal regulation of dopamine efflux does not account for the behavioral effect. However, the D₂-like dopamine receptor antagonists haloperidol and raclopride, but not the D₁-like dopamine receptor antagonist SCH23390, blocked the amphetamine-induced reduction in locomotor activity in coloboma mice, providing direct evidence that D₂-like dopamine receptors mediate the effect of amphetamine in these mice. With the precedent established that it is possible to directly antagonize this response, this strategy should prove useful for identifying novel therapeutics in ADHD and tends to support DART.

This concept is in agreement with other clinically directed research suggesting a number of treatments sharing common mechanisms of action. Herridge and Gold [250] suggest a smorgasbord of neurochemical activators including the alpha 2-adrenergic agonists, such as clonidine and guanabenz, act to block noradrenergic activity in the locus coeruleus and therefore block the negative reinforcement of opioid withdrawal; Naltrexone, to prevent the positive reinforcement of administered opioids by blocking them from binding to the opioid receptor; in cocaine addiction, most of the agents (e.g. bromocriptine) focus on decreasing the severity of the immediate withdrawal symptoms potentiating dopaminergic transmission and in so doing tend to counter the dopamine depletion effect of prolonged cocaine use. Desipramine and perhaps other antidepressants may have a special role in treating cocaine addiction and relapse by affecting dopaminergic transmission. The “dopamine hypothesis” suggested by Dackis and Gold [251] involving cocaine addiction certainly would support out neurogenetic explanation of relapse. Other studies throughout the years have supported this concept especially for psychostimulant relapse behavior [252–254] and for the analgesic Fentanyl a potent mu-opioid receptor agonist [255]. The role of stress in Nicotine relapse and specifically CRF(1) receptors but not CRF(2) receptors play an important role in the anhedonic state associated with acute nicotine withdrawal and stress-induced reinstatement of nicotine-seeking (relapse) [256–257]. Finally, it is well known that discontinuation of chronic and excessive alcohol consumption leads to a dysphoric state in humans. Most recently studies in rats show that a 12 week discontinuation of a liquid 10% diet in rats leads to a pronounced deficit in brain reward function and acute and protracted anxiety-like behavior in rats. Taken together these findings provide neurochemical rationale for DART [258]

While Dupont *et al* [259] found 80% recovery at 5 years in a nationwide survey of physicians under being mandated to be drug free or potentially losing their medical license may not do anything in terms of their biological “wanting “ and liking psychoactive substances. Future warranted translational research with positive outcome in preventing

relapse due to dopamine supersensitivity [260] in Reward Deficiency Syndrome (RDS) with neurochemical rebalancing of D₂ receptors by dopaminergic agonist therapy will ultimately support our concept termed “Deprivation- Amplification Relapse Therapy (DART).

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Figure 1. Dopaminergic Polymorphisms Causes Serious Relapses After Long Drug Abstinence

Figure 1. Dopaminergic polymorphisms cause serious relapse after long drug abstinence

The figure shows the hypothesis underlying pathways and mechanisms of relapse after a long period of drug abstinence. The figure demonstrates that after prolonged abstinence, the re-imbining of drugs induces serial events that can precipitate relapse in drug abusers. To date there has been no reasonable comprehensive biogenetic explanation to explain this well-known clinical phenomenon. The authors propose that this clinically observed event is a result of super-sensitivity and may be related to dopaminergic polymorphisms.

Figure 2. Schematic view showing the Pre synapse and Post Junctional Dopamine Neurons and Dopamine Receptor Density

Figure 2. Schematic view of dopaminergic genetics and post-junction receptor density

The figure illustrates pre- and post-junction dopamine neurons and the dopamine receptor density being low due to the DRD₂ A1 allele probands, compared to probands positive for the DRD₂ A2 allele with a normal complement of D₂ receptor density. This phenomenon mimics the well-known physiological mechanism “Denervation Supersensitivity”. Thus, A1 allele carriers may have “Deprivation Amplification” at the reward site in contrast to the A2 carriers, who would have a normal response to re-imbibing a psychoactive D₂ agonist. It is proposed that relapse is worse for carriers of the A1 allele compared to the A2 allele of DRD₂ gene.

Figure 3. Strong dopaminergic and amplified D₂ reward circuitry

Measures of fMRI activation indicate that after strong dopaminergic agonist therapy like bromocriptine, reward circuitry activity is amplified in DRD₂ A1 allele carriers [166]. Moreover, *in vitro* studies demonstrated that under chronic or long-term therapy of bromocriptine, a D₂ agonist, there was a significant proliferation of D₂ receptors [243, 244]. This seems to lead to a positive outcome [91] and better treatment compliance [226]. Moreover, low D₂ receptor density and polymorphisms of the D₂ gene have been significantly associated with risk for relapse of various psychoactive drugs of abuse. It is proposed herein that the enhanced sensitivity following strong dopaminergic D₂ receptor activation may be due in part to the "Denervation Supersensitivity" phenomenon. Administration of DRD₂ agonists (e. g. Synaptamine complex KB220™) will target D₂ sensitization and this will attenuate relapse especially in D₂ receptor A1 allele carriers.

Key Common Neurocircuitry Elements in Drug Seeking Behavior of Addiction

Figure 4. Summary of neurocircuitry involved in addictions

This figure shows three potential circuits active during addiction and drug abuse. These are: (1) Reward Circuit, consisting of the nucleus accumbens and extended amygdala (bed nucleus of the stria terminalis and central nucleus of the amygdala); (2) "Craving" Circuit, consisting of the dorsal prefrontal cortex, and basolateral amygdala; and (3) "Compulsivity" Circuit, consisting of a loop of connections involving the ventral striatum, ventral pallidum, medial thalamic region, and orbitofrontal cortex. The circuitry is interconnected and interactive. With permission from Gene Therapy Press.

Table 1

Recovery rates for poly-drug abusers utilizing Synaptamine™ variant complex {KB220} in long term out-patient therapy.

Drug of Choice	San Francisco ¹ (% Recovery)	Las Vegas ² (%Recovery)
Alcohol	73	93
Opiates	N/A	100
Cocaine	53	N/A *
Poly-drug **	63	96.5

Total Relapse rate for both studies = 20.25 %

Total Recovery rate for both studies = 79.75%

¹Brown *et al.* J Psychoactive Drugs, 1990 -This was a study involving X DUI offenders in an out-patient program whereby a Synaptamine™ variant was administered for a 10 month period.

²Chen *et al.* Adv Ther, 2007 – This was a study involving 76 criminal justice system and federal government probates whereby a Synaptamine™ variant was administered for a 12 month period.

* In the Las Vegas study all psychostimulant abusers (small number n-15) also abused alcohol preventing analysis.

** Poly-drug refers to the combination of both study 1 and 2.