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

Abstract

**Background and Hypothesis:** It is well known that after prolonged abstinence, individuals who use their drug of choice experience a powerful euphoria that often precipitates relapse. While a biological explanation for this conundrum has remained elusive, we hypothesize that this clinically observed “supersensitivity” might be tied to genetic dopaminergic polymorphisms. Another clinical feature 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 with DRD2 A2 allele carriers. Because 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 D2 agonist bromocriptine. Moreover, under chronic or long-term therapy with D2 agonists, such as bromocriptine, it has been shown in vitro that there is a proliferation of D2 receptors. One explanation for this relates to the demonstration that the A1 allele of the DRD2 gene is associated with increased striatal activity of L-amino acid decarboxylase, the final step in the biosynthesis of dopamine. This appears to be a protective mechanism against low receptor density and would favor the utilization of an amino acid neurotransmitter precursor like L-tyrosine for preferential synthesis of dopamine. This seems to lead to receptor proliferation to normal levels and results in significantly better treatment compliance only in A1 carriers. **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.” Rats with unilateral depletions of neostriatal dopamine display increased sensitivity to dopamine agonists estimated to be 30 to 100 × in the 6-hydroxydopamine (6-OHDA) rotational model. Given that mild striatal dopamine D2 receptor proliferation occurs (20%–40%), it is difficult to explain the extent of behavioral supersensitivity by a simple increase in receptor density. 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 amino acid neurotransmitter precursors, enkephalinase, and catechol-O-methyltransferase (COMT) enzyme inhibition, which have resulted in attenuated relapse rates in reward deficiency syndrome (RDS) probands. If future translational research reveals that dopamine agonist therapy reduces relapse in RDS, it would support the proposed concept, which we term “deprivation-amplification relapse therapy” (DART). This term couples the mechanism for relapse, which is “deprivation-amplification,” especially in DRD2 A1 allele carriers with natural D2 agonist therapy utilizing amino acid precursors and COMT and enkephalinase inhibition therapy.

**Keywords:** addiction; reward circuitry; dopamine; neurogentics; deprivation-amplification relapse therapy
Background

The relapse rates for patients with substance use disorder are high worldwide and in a number of cases the reuse of psychoactive substance following prolonged abstinence may even be fatal. The mechanism by which this phenomenon occurs has been elusive. This article provides a novel genetic mechanism tied to a potential solution. We propose that low D2 receptor density and polymorphisms of the DRD2 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 amino acid neurotransmitter precursors, enkephalinase, and catechol-O-methyltransferase (COMT) enzyme inhibition, which have resulted in attenuated relapse rates in reward deficiency syndrome (RDS) probands. If future translational research reveals that dopamine agonist therapy reduces relapse in RDS, it would support the proposed concept, which we term “deprivation-amplification relapse therapy” (DART). This term couples the mechanism for relapse, which is “deprivation-amplification,” especially in DRD2 A1 allele carriers with natural D2 agonist therapy utilizing amino acid precursors and COMT and enkephalinase inhibition therapy.

In 1996, our laboratory first described RDS to define a common genetic variant involving dopamine D2 receptor gene (DRD2) polymorphisms1–4 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, addiction, related aberrant reward behaviors (eg, carbohydrate craving), and creative function.11–19 The Taq1 A1 allele of this gene also may be involved in comorbid antisocial personality disorder symptoms,20 high novelty seeking,21–23 and alcoholism.24 Addiction is increasingly recognized as one disease that shares a common neuroanatomy25 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 RDS. Reward deficiency syndrome is a general condition or umbrella disorder2,4,33,34 that tends to increase the risk for subsequent drug-seeking behavior35,36 as well as conditions such as attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, and antisocial personality symptoms.3,37–40 Reward deficiency syndrome refers to the breakdown in a cascade of neurotransmitters—the reward cascade48 in the brain in which one reaction triggers another—promoting intense cravings and resultant aberrant conduct, which are 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 (eg, 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 in D2 receptors then predisposes individuals to a high risk for multiple addictive and impulsive behaviors.5,70,71

This deficiency in dopamine receptors may set up a physiological desire for dopamine and place an individual at high risk for RDS behaviors. Although other neurotransmitters (eg, glutamate, gamma-aminobutyric acid [GABA],72 serotonin,73 and enkephalins74) may be important in determining the rewarding and stimulating effects of substances, and 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 between 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 the 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 relation.1,2,4,33,34 A careful review of the negative studies reveal that in many cases the investigators have not incorporated rigorous screening of controls: utilizing nonsevere cases of alcoholism, eliminating subjects with liver enzyme abnormalities, small sample size, and utilization of controls carrying RDS behaviors. This reduced statistical power between the phenotype and nonphenotype disorder.

The Taq1 A1 allele has been associated with low dopamine D2 receptor density in alcoholics.87 Moreover, other studies have confirmed that the striatal postsynaptic D2 receptor densities are low among alcoholics.136 It is noteworthy that PET studies, while important, paint a fairly incomplete picture in that this technique does not allow...
the investigator to know whether low binding is due to an altered basal dopamine neuronal level or low D2 receptor density. The dopamine transporter system is involved in clearing dopamine from the synapse, affecting reward sensitivity, and studies of presynaptic and postsynaptic 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.\(^{137}\) The resultant effect would be a reduced amount of dopamine in the synapse because the high density of DAT sites would quickly remove the synaptic dopamine back into the presynaptic neuronal vesicles. Another study, using the highly selective radioligand PE2I,\(^{140}\) found lower DAT densities among alcoholics versus 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 they found a nonspecific “reward” gene. Moreover, the DRD2 Taq1 A allele as well as the 957C allele have suggested an underlying dopaminergic defect.\(^{137-141}\) The results are interpreted as reflecting a specific sensitivity to stress and anxiety,\(^{82,142-146}\) and both symptoms have been associated with sensitivity.\(^{137-141}\) The sensitivity is elevated in high-anxiety subjects compared with low-anxiety subjects. Further, other RDS and related neurological and psychiatric disorders are also found to be associated with polymorphisms of the DRD2 gene.

**Hypothesis**

Grasping the mechanism that motivates 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 (eg, food and sex).\(^{155-157}\) The distinction between “natural rewards” and “unnatural rewards” is important. Natural rewards include satisfaction of physiological drives (eg, hunger and reproduction). 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 to the fact that this breakdown of the reward system in genetically prone individuals may lead to the acquiring of unnatural rewards. Reward deficiency syndrome 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.\(^{152}\)

Dopamine has been associated with pleasure and has been called the “antistress molecule” and/or the “pleasure molecule,” mediating nondrug behaviors such as sex and gambling.\(^{2,82,163-165}\) When dopamine is released into the synapse, it stimulates a number of receptors (D1–D5) which results in increased feelings of well-being 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 noted, persons carrying an A1 allele are thought to have a lower D2 receptor density and a higher risk of substance abuse.

One study was designed to investigate the influence of the DRD2 Taq1A 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 (nucleus accumbens [NAc]) from placebo to bromocriptine only in subjects carrying the A1 allele. Further, only A1 carriers showed an increase in 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 carriers of the A1 allele.\(^{92}\)

This finding may seem paradoxical due to having low dopamine D2 receptors in DRD2 A1/A2 and A1/A1 allele carriers compared with DRD2 A2/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 explanation of this paradox (Figures 1–3).

**Denervation Supersensitivity: Supporting Evidence for DART**

We propose the use of DART as a novel adjunct in the treatment of addictive disorders. Deprivation-amplification relapse therapy 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 (ie, “a fix”) that precipitates serious relapse.\textsuperscript{25,26} If the ideas proposed herein are confirmed, DART could become a putative modality to help prevent relapse, especially in D2 receptor-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. 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 reduction 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 lifelong 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, in association with perhaps different neuronal phenotypes, and with greater incidence in either intact (D2)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Dopaminergic polymorphisms cause serious relapse after long-term drug abstinence.}
\end{figure}
or dopamine-reduced counterparts (D1). There are multiple physiological consequences of receptor supersensitivity. In this regard, we are also proposing that D2 receptor supersensitivity occurs in DRD2 A1 allele carriers at birth; thus, the individual is at high risk for developing substance use disorder in adulthood (a clinical subtype of RDS).

One example of this concept comes from earlier work. Research has 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 that initiates contraction by means of depolarizing the cell membrane. Work from the laboratory of Westfall indicates that altered electrical properties are not the only postjunctional changes that can account for the enhanced response. Dose-response curves for stimulant agonists were obtained in isolated vasa deferentia, which were depolarized by a potassium-rich, sodium-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 that is not taken up by the neuronal amine transport system. Pretreatment of rats with reserpine (1 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 to any agonist. This phenomenon has been confirmed by a series of experiments reported by Blum’s group, which also involved the vas deferens and supersensitivity to norepinephrine after ethanol and cannabis in utero. Therefore, it is feasible that when there is a low density (A1 carriers) of postjunctional D2 receptors compared with a higher “normal” compliment of D2 receptors (A2 carriers), just as in denervation, powerful D2 agonists like bromocriptine (unlike weak nonspecific dopamine releasers like glucose, binding

Figure 2. Schematic view of dopaminergic genetics and postjunction receptor density.
to 5 dopamine receptors) induce 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 on 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, stress, and by priming injections of the drugs themselves, events also known to trigger drug craving in 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 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 NAc. In contrast, compounds that activate D1 receptors prevent relapse to drug-seeking behavior, possibly through satiation of reward pathways. Chronic neuroadaptations in dopamine receptor signaling pathways in the NAc 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 neuroadaptations 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 treatments.
compounds to treat drug addiction. We further postulate that the dopamine sensitization during abstinence may occur when the D2 receptors are compromised as in the case of DRD2 A1 allele carriers. This notion is supported in part by the work of Li et al. Subjective craving is considered to be a central phenomenon, which contributes to the continuation of drug use in active abusers 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 et al. study was to test the hypothesis that heroin addicts carrying specific variants in dopamine-related genes would have greater craving following exposure to a heroin-related cue. Craving induced by a series of exposures to heroin-related cues was assessed in a cohort of Chinese heroin abusers (N = 420) recruited from a natural abstinence center in Shanghai, China. Significantly stronger cue-elicited heroin craving was found in individuals carrying D2 dopamine receptor gene (DRD2) TaqI RFLP A1 allele than in the noncarriers (P < 0.001). Moreover, they did not observe significant association of cue-elicited craving with the 9-repeat allelic variants in dopamine transporter gene (DAT) SLC6A3 or with the dinucleotide repeat polymorphism (DRP) 148bp allele in D5 dopamine receptor gene (DRD5). These results 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. Further, this phenomena was not specific to just heroin. Ujike also found that the risks of rapid onset of methamphetamine psychosis, worse prognosis, and the complication of spontaneous relapse are associated with polymorphisms of the dopamine D2 receptors, monoamine oxidase-A, catechol-O-methyltransferase, among other related genes. In addition, Perkins et al. found similar evidence for a correlation between both the DRD2 and OPRM1 genes and nicotine (smoking behavior). They found an increase in smoking amount owing to negative mood, which was associated with: dopamine D2 receptor (DRD2) C957T (CC > TT or CT), SLC6A3 (presence of 9 repeat > absence of 9). 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. in an elegant gene therapy study. It is well known that chronic cocaine use reduces glutamate levels in the 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 relation between neuroplasticity in AMPA receptors and the behavioral manifestation of cocaine addiction remains unclear. Bachtell et al. examined the behavioral effects of upregulating and downregulating 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 receptor, but not D1 receptor-mediated behavioral responses. As a correlate of the sensitization experiments, the researchers overexpressed wt- or pd-GluR1 in the NAc core during cocaine self-administration, and tested the effects on subsequent drug-seeking behavior 3 weeks after overexpression declined. wt-GluR1 overexpression 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 overexpressed 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. Collectively, 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 alcohol relapse as well.

**Deprivation-Amplification Relapse Therapy**

As noted, relapse of psychoactive drug use may be due to specific genetic polymorphic antecedents. However, because 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 mesolimbic 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.179–181 There is also evidence implicating prefrontal cortex glutamate (GLUT)-containing neurons, some of which are known to project to NAc and 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_A 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 nondopamine interneurons.196–202 Local VTA GABA_A and GABA_B receptor activation has been shown previously to modulate dopamine transmission in NAc and VTA.

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. Data suggest that the relevant GABA_B receptors are located on dopamine neurons, whereas the GABA_A receptors are located on GABA interneurons and, perhaps, also on dopamine cells. The finding related to stress reduction by Synaptamine™ Complex [KB220] (LifeGen, Inc., San Diego, CA) 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 to 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 Yet, 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 al16 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-blind, placebo-controlled, randomized study of inpatients, Blum et al201 analyzed the stress-relieving effects of Synaptamine™ Complex [KB220], 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 A1 allele polymorphisms have been correlated with susceptibility to depressive symptoms during stressful life events. These results support a role for DRD2 as a susceptibility gene for alcohol dependence within multiplex families at high risk for developing alcohol dependence224 and more severe stress or stress disorders.209,225 Moreover, our research and that of others 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

As noted 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 similar findings.91 Further, only A1 carriers showed an increase of performance under bromocriptine. The results are interpreted as reflecting a specific sensitivity to 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.\textsuperscript{226,227} Stress is a well-known risk factor for addiction onset and relapse. 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 one’s extent of the severity of stressful events.\textsuperscript{209,225} The effects of these alterations on the corticostriatial-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.\textsuperscript{228}

Moreover, 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 overactivity 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\textsuperscript{229} provide 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 comorbidity 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 controls using the Perceived Stress Scale and repeated morning salivary cortisol levels over 3 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 after discharge from inpatient treatment was also conducted. Fox et al.\textsuperscript{230} found that cocaine-dependent patients showed higher levels of distress compared with controls according to Perceived Stress Scale scores and cortisol levels. They also demonstrated a significantly reduced learning curve, 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. 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.\textsuperscript{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 by 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 inpatients undergoing treatment. In fact, it may have profound influence on the well-known treatment phenomena called withdrawal against medical advice (WAMA) rate. It is of note that stress may induce WAMA rates by virtue of disrupting reconsolidation of drug-related memory. In other studies, our laboratory has shown the significant decrease in WAMA rate in inpatient cocaine-dependent patients administered a...
Synaptamine™ variant [KB220].232,233 Thus, one proposed mechanism is that KB220 prevented WAMA rate because of its putative antistress property, thereby allowing for normalized reconciliation drug-related memory to occur.

Stress-associated effects of dopamine D2 receptor polymorphisms have been intensely studied. Gilbert et al234 found that nicotine replacement therapy (NRT) reduced personality traits related to a negative effect. A negative effect was found to a greater extent in DRD2 A1 carriers than in A2/A2 individuals during the first 2 weeks of treatment (when on the 21-mg patch); however, A1 carriers experienced a renewal of negative-effect symptoms when switched to the 7-mg patch and when off the patch, while A2A2 individuals continued to benefit from NRT. Other work by Comings’s group209 found a significant interaction between DRD2 genotype and stress score as a predictor of Michigan Alcoholism Screening Test (MAST) score in alcoholics. Additionally, this difference was found to be largely accounted for by the Hispanic Stress Inventory (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 4 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 (Figure 4).

In a recent paper, Koob235 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

![Figure 4. Summary of neurocircuitry implicated in addictions.](image)

**Key Common Neurocircuitry Elements in Drug Seeking Behavior of Addiction**

- **Drug-Seeking Behavior**
  - Motor Cortex
  - Orbitofrontal Cortex
- **Drug-Associated Reinforcement**
  - Reward and Stress
  - Basolateral Amygdala Complex
  - Bed Nucleus of Stria Terminalis
  - Ventral Pallidum
- **Behavioral Output**
  - Compulsivity
  - Ventral Striatum
  - Ventral Pallidum
  - Thalamus
  - Nucleus Accumbens
- **Drug and cue Reinstatement**
  - Craving
  - Dorsal Prefrontal Cortex (Anterior Cingulate, Prelimbic Cortex)

This figure shows 3 potential circuits active during addiction and drug abuse: 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.
properties 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, nonpowerful manner should result in an enhanced D2 proliferation even in DRD2 A1 probands.

In one supportive example, although bupropion and NRT are efficacious tobacco-dependence treatments, there is substantial inter-individual variability in therapeutic response, and most smokers relapse. Pharmacogenetic research may improve treatment outcomes by identifying genetic variants predictive of therapeutic response. Lerman et al. investigated the roles of 2 functional genetic variants in the DRD2 gene in response to pharmacotherapy for tobacco dependence among participants in 2 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 versus nicotine nasal spray (N = 368). At the end of treatment, a 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 with those carrying a Del C allele. By contrast, smokers carrying the Del C allele had significantly (P = 0.006) higher quit rates on NRT compared with those homozygous for the Ins C allele, independent of type of NRT. The C957T variant was also associated (P = 0.03) with abstinence following NRT. These data suggest that bupropion may be the preferred pharmacologic treatment for smokers homozygous for the DRD2-141 Ins C allele, while NRT may be more beneficial for those who carry the Del C allele. These results once again support the role of the DRD2 gene polymorphisms in relapse risk as well as support the use 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 2 outpatient studies. Brown et al. studied driving under the influence (DUI) offenders with either alcohol- or cocaine-related problems. 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 outpatient study by Chen et al., 239 76 patients (45 males and 31 females; mean age, 33 years [standard deviation, 7.0]) diagnosed with a serious substance use disorder were recruited. After excluding 15 patients who dropped out before the end of the study, self-reported craving decreased from program entrance to 12 weeks (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 < 0.001). Building up to relapse scores (each of 5 individual items and summary value) showed similar improvement after 1 year of treatment; the mean decrease in scores was significant for stress (t = 3.3; P = 0.002), depression (t = 4.0; P < 0.001), anger (t = 4.4; P < 0.001), anxiety (t = 4.5, P < 0.001), drug craving (t = 5.4, P < 0.001), and summary building up to relapse (t = 4.1; P < 0.001). Also, recovery score measures of energy level (t = 8.4; P < 0.001) and ability to refrain from drug-seeking behavior (t = 7.4; P < 0.001) showed significant mean increases from entry to 1 year. During the study, the alcoholic dropout rate was only 7% (4 of 57), and the opiate abuses had a dropout rate of 0%.

A summary of this data suggests that utilization of a putative D2 agonist could ultimately lead to a reduction of relapse rates to only 20% (Table 1). Other studies also utilizing Synaptamine™ variants result in positive anti-drug-seeking behavior and ability to refrain from drug-seeking behavior (t = 7.4; P < 0.001) showed significant mean increases from entry to 1 year. During the study, the alcoholic dropout rate was only 7% (4 of 57), and the opiate abuses had a dropout rate of 0%.

Table 1. Recovery Rates for Polydrug Abusers Utilizing Synaptamine™ Complex [KB220] in Long-term Outpatient Therapy238,239

<table>
<thead>
<tr>
<th>Drug of Choice</th>
<th>San Francisco238 (% Recovery)</th>
<th>Las Vegas239 (% Recovery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>73</td>
<td>93</td>
</tr>
<tr>
<td>Opiates</td>
<td>N/A</td>
<td>100</td>
</tr>
<tr>
<td>Cocaine</td>
<td>53</td>
<td>N/A*</td>
</tr>
<tr>
<td>Polydruga</td>
<td>63</td>
<td>96.5</td>
</tr>
</tbody>
</table>

Total recovery rate for both studies = 20%. Total recovery rate for both studies = 80%.

238Brown et al. This was a study involving DUl offenders in an outpatient program whereby a Synaptamine™ variant was administered for a 10-month period.
239Chen et al. This was a study involving 76 criminal justice system and federal government probates whereby a Synaptamine™ variant was administered for a 12-month period.

aIn the Las Vegas study all psychostimulant abusers (small number n = 15) also abused alcohol, preventing analysis.

Polydrug refers to the combination of both studies.
of psychostimulants in (ADHD) are not well understood, but indirect evidence implicates D2 dopamine receptors. Fan and Hess\textsuperscript{249} dissected the components of dopaminergic neurotransmission in the hyperactive mouse mutant Coloboma to identify presynaptic 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 that share common mechanisms of action. Herridge and Gold\textsuperscript{250} suggest a smorgasbord of neurochemical activators including the alpha 2-adrenergic agonists, such as clonidine and guanabenz. These act to block noradrenergic activity in the locus coeruleus and therefore block the negative reinforcement of opioid withdrawal. Naltrexone is used to prevent the positive reinforcement of administered opioids by blocking them from binding to the opioid receptor. In cocaine addiction, most of the agents (eg, 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\textsuperscript{251} involving cocaine addiction certainly would support out neurogenetic explanation of relapse. Other studies have supported this concept, especially for psychostimulant relapse behavior\textsuperscript{252–254} and for the analgesic fentanyl, a potent mu-opioid receptor agonist.\textsuperscript{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).\textsuperscript{256,257} Finally, it is well known that discontinuation of chronic and excessive alcohol consumption leads to a dysphoric state in humans. Other work also supports the relationship between dopaminergic activation by agonists and D2 genotypes. For example, food reinforcement (eg, glucose, a D2 agonist) was greater in obese than in nonobese individuals, especially in obese individuals with the Taq1 A1 allele.\textsuperscript{258} 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.\textsuperscript{259} Taken together, these findings provide neurochemical rational for DART.

It is noteworthy that DuPont et al\textsuperscript{260} found 80\% recovery at 5 years in a nationwide survey of physicians mandated to be drug-free or potentially lose their medical license. Although this represents a rather high recovery rate, it does not address the fact that these individuals may still be biologically prone to and have wanting or liking (craving) behaviors toward psychoactive substances. Untreated craving behaviors could be diverted to other nonpsychoactive-seeking RDS behaviors, such as overeating, gambling, smoking, and/or drinking alcohol. In the future, if translational research reduces relapse due to dopamine supersensitivity\textsuperscript{261} in RDS, with neurochemical rebalancing of D2 receptors by dopaminergic agonist therapy, it would support our concept, DART; in addition, the nicotinic acetylcholine receptor using varenicline, a partial alpha-4 beta nicotinic acetylcholine receptor agonist and an alpha-7 full agonist, could be shown to reduce relapse in smoking behavior. Pharmacological evaluation of nicotine-stimulated dopamine release from striatum has yielded data consistent with activation of a single population of nicotinic acetylcholine receptors (nAChR). However, discovery that alpha-conotoxin MII (alpha-CtxMII) partially inhibits the response indicates that 2 classes of presynaptic nAChRs mediate dopamine release.\textsuperscript{262} Confirmation using either D2 agonist therapy and/or nicotinic acetylcholine receptor agonist therapy, or even a combination, may be quite informative and reduce relapse in RDS.

Using PET scans in monkey cocaine self-administration studies, Nader and Czoty\textsuperscript{263} found an inverse relationship between D2 receptor availability and vulnerability to the reinforcing effects of cocaine. Environmental variables can increase or decrease D2 receptor binding in an orderly fashion, and the resulting changes in D2 function influence the vulnerability to abuse cocaine. In maintenance, chronic cocaine exposure produces decreases in D2 receptor binding, which may be a mechanism that contributes to continued drug use and relapse. Finally, during abstinence there are individual differences in rates of recovery of D2 receptor availability. The authors suggest that D2 receptor density is a predictive
factor in triggering relapse. This finding further supports the goal of achieving DART to prevent relapse.

Despite numerous efforts to dissect the mechanism responsible for dopamine supersensitivity, no consensus has been reached to date.\textsuperscript{1,264} We believe that at least the understanding of potential genetic antecedents, such as carrying the DRD2 A1 allele, provides an important contribution to the existence of high risk for relapse. Rats with unilateral depletions of neostriatal dopamine display increased sensitivity to dopamine agonists estimated to be 30 to 100 x in the 6-hydroxydopamine (6-OHDA) rotational model. Given that mild striatal dopamine D2 receptor proliferation occurs (20\%-40\%), it is difficult to explain the extent of behavioral supersensitivity by a simple increase in receptor density.\textsuperscript{264,265} Our suggestion would be to couple genotyping with DART as described in this commentary, especially in RDS patients.

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 with DRD2 A2 allele carriers. We posit that this clinically observed “supersensitivity” may be tied to genetic dopaminergic polymorphisms. Based on the fact that carriers of the A1 allele relative to carriers of 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 DRD2 gene are associated with risk for relapse of substance and other RDS behaviors. 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-methyltransferase (COMT) enzyme inhibition, which have resulted in attenuated relapse rates in RDS probands. Future research with positive outcomes showing prevented or lower relapse in RDS will ultimately support our proposed concept of DART.

Acknowledgments

The authors would like to thank the staff at Path Research and Medical Foundation, New York as well as financial support. The authors acknowledge the financial support of Electronic Waveform Lab of Huntington Beach, CA. The authors appreciate the editorial review and contribution of Margaret Madigan. The writing of this review was supported in part by funds from the US Department of Health Services, NIAA (R01-AA07112 and K05-AA00219) and the Medical Research Service of the US Department of Veterans Affairs to Marlene Oscar-Berman.

Conflict of Interest Statement

Kenneth Blum, PhD, Roger L. Waite, DC, and William Downs, BSc are Officers for LifeGen, Inc., San Diego, CA. LifeGen, Inc. has the worldwide distribution rights of the Synaptamine™ Complex (KB220). Siobhan Morse, MHSA is a paid employee of G and Holistic Addiction Treatment Center of North Miami Beach Florida whereby a Synaptamine™ Complex [KB220]™ is utilized for the adjunctive treatment of patients. John Giordano, MAC, PhD (Hon) is co-owner of G and Holistic Treatment Center. Thomas J.H. Chen, PhD, Abdalla Bowirrat, MD, PhD, Eric R. Braverman, MD, Margaret Madigan, RN, Marlene Oscar-Berman, PhD, Nicholas DiNubile, MD, Eric Stice, PhD, and Mark Gold, MD disclose no conflicts of interest.

Resource Information

The following Web site links are suggested for additional information: http://www.addictionsearch.com and http://www.drugstrategies.org.
References


124. Gelernter J, Grandy DK, Bunzon J. D2 dopamine receptor locus (probe H2G1) maps close to D11S29 (probe L7) and is also linked to BPBD (probe PBBD0.0) and D11S84 (probe p-2-7-ID6) on 11q. *Cytogetic Cell Genet*. 1989;51:1002.


146. Johnson K. The dopamine D2 receptor as a candidate gene for alcoholism. A thesis submitted in partial requirement for the degree of Bachelor of Science (Hons). School of Community Medicine, University of New South Wales, Australia. February, 1996.


158. Hodge CW, Cox AA. The discriminative stimulus effects of ethanol are mediated by NMDA and GABA (A) receptors in specific limbic brain regions. Psychopharmacol (Berl). 1999;139(1–2):95–107.


186. Moghaddam B. Stress preferentially increases extraneuronal levels of excitatory amino acids in the prefrontal cortex: comparison to hippocampus and basal ganglia. J Neurochem. 1993;60(5):1650–1657.


