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Pharmacogenetic Treatments for Drug Addiction:

Cocaine, Amphetamine and Methamphetamine

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Abstract

Background—Pharmacogenetics uses genetic variation to predict individual differences in response to medications and holds much promise to improve treatment of addictive disorders.

Objectives—To review how genetic variation affects responses to cocaine, amphetamine, and methamphetamine and how this information may guide pharmacotherapy.

Methods—We performed a cross-referenced literature search on pharmacogenetics, cocaine, amphetamine, and methamphetamine.

Results—We describe functional genetic variants for enzymes dopamine-beta-hydroxylase (DβH), catechol-*O*-methyltransferase (COMT), and dopamine transporter (DAT1), dopamine D4 receptor, and brain-derived neurotrophic factor (BDNF). A single nucleotide polymorphism (SNP; C-1021T) in the DβH gene is relevant to paranoia associated with disulfiram pharmacotherapy for cocaine addiction. Individuals with variable number tandem repeats (VNTR) of the *SLC6A3* gene 3′-untranslated region polymorphism of DAT1 have altered responses to drugs. The 10/10 repeat respond poorly to methylphenidate pharmacotherapy and the 9/9 DAT1 variant show blunted euphoria and physiological response to amphetamine. COMT, D4 receptor, and BDNF polymorphisms are linked to methamphetamine abuse and psychosis.

Conclusions—Disulfiram and methylphenidate pharmacotherapies for cocaine addiction are optimized by considering polymorphisms affecting DβH and DAT1 respectively. Altered subjective effects for amphetamine in DAT1 VNTR variants suggest a ‘protected’ phenotype.

Scientific Significance—Pharmacogenetic-based treatments for psychostimulant addiction are critical for successful treatment.

Keywords

Gene variants; pharmacotherapies; drug therapy; stimulants; individualized therapy; gene-based therapeutics; polymorphisms; genetic variation; subjective effects; drug dependence; addiction psychiatry

INTRODUCTION

New technology in molecular biology, pharmacology, and genomics research has transformed the way pharmacotherapeutic medications are administered in clinical practice. Variability in drug pharmacokinetics and pharmacodynamics are largely influenced by an individual’s

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genetic makeup (1,2). Thus, the goal of pharmacogenetics is to correlate drug response with genetic makeup. In theory, individualizing therapy based on genetic profile will optimize responses to therapies and help better define common "polygenetic" diseases into more discrete molecular-genetic disorders (3-6). Indeed, recent pharmacogenetic studies in clinical medicine confirm that individual's genetic profile is a much better guide for drug choice that leads to improved clinical outcome (3-13). The present challenge however is integrating these advances into mainstream medicine (1,14).

Initial pharmacotherapy choices for psychiatric diseases fail in 30-40% of patients and a large portion of responders may be due to the placebo effect (15,16). Taking into account genetic individual variability can improve initial medication choices (17-19). For example, the hepatic cytochrome P450 system metabolizes a majority of psychiatric medications and shows 10% genetic variability (20). Considering this variability can help avoid producing high systemic drug levels that result in serious adverse side effects and noncompliance (18,20-22). Other adverse side effects such as weight gain and dyskinesias are also linked to gene variants (23, 24).

Recent studies in psychiatry give clear evidence that tailoring drug treatment to a person's genetic makup is critical to engendering a positive therapeutic response (25), thwarting dangerous side effects due to toxicity (17,20,21) and increasing compliance (18). Less attention however has been centered on drug dependence likely because addictions have fewer effective medications so less opportunity has arisen for pharmacogenetic studies. Drug addictions are common polygenic, chronic, relapsing brain disease whose pharmacotherapy would benefit from becoming more optimally defined through molecular-genetic approaches (15,26-28). Clearly, not all that experiment with drugs of abuse become addicted. This heterogeneity of response to developing addiction can be attributed, in part, to genetically driven inter-individual differences (29,30). Mutations in genetic code may be responsible for differences in the subjective effects of drugs of abuse making them either more rewarding or aversive depending on the individual's genotype. Genetically divergent and genetically altered rats, mice (31-33) and human studies support this notion (30,34,35).

Gene profiling of individuals who respond divergently to drugs of abuse may help medication development or help guide present pharmacotherapy. For example, genetically driven alterations in enzymes (DβH, COMT), transporters (DAT1) receptors (D4) and neuropeptides (BDNF) alter psychostimulant effects and response to medications aimed at these targets. Thus, this review of pharmacogenetics extends our previous coverage of alcohol and opiates to psychostimulants and follows that review's goal of identifying possible pharmacogenetic targets (36).

DRUG DEPENDENCE: NEUROBIOLOGICAL SUBSTRATES

The motivating effects of drugs of abuse are mediated through multiple sites and mechanisms in the brain but studies strongly support activation of the mesocorticolimbic dopamine (DA) system as key to mediating their reinforcing effects (32,36) (33,37-39). DAergic cell bodies in the ventral tegmental area (VTA) and their projections to the prefrontal cortex (PFC) and nucleus accumbens (NAC) define the core circuitry of this system whereas the amygdala, hippocampus and hypothalamus are associated with emotional memories with drug addiction (40-43). Further, drugs of abuse evoke DA release in the PFC and NAC and lesion studies of these brain areas alters their behavioral effects (44-47).

Figure 1 presents a detailed hypothetical scenario for a DA neuron and its target neuron. DA from terminal regions binds to a number of DA receptor subtypes called D1-like (D1, D5) or D2-like (D2, D3, D4) classified based on molecular and pharmacological attributes. Synaptic DA's action is terminated by sequestration of the transmitter into the presynaptic neuron

through the DA transporter (DAT) (48,49). DAT levels are high in ventral midbrain and striatum but low in the PFC where the enzyme catechol-*O*-methyltransferase (COMT) inactivates released DA through enzymatic conversion (50-52). Activation of D1-like receptors leads to increasing amounts of the second messenger cAMP (cyclic adenosine 3′5′-monophosphate) through stimulation of adenylate cyclase via G_s stimulatory G-proteins whereas D2 activation acting through G_i inhibitory G-proteins decreases the formation of cAMP. The formation of cAMP is dependent upon adenylate cyclase and degraded by phosphodiesterase enzymes in the cytoplasm. Increased cAMP levels affect intracellular protein kinase A (PKA). The catalytic subunit of PKA (PKA-Cα) may translocate to the nucleus of the cell where it phosphorylates the transcription factor cAMP-dependent protein kinase (CREB) leading to CRE (cAMP response element)-mediated gene expression (53). PKA-Cα also phosphorylates dopamine and cAMP regulated phosphoprotein 32 kDa (DARPP-32) that has numerous intracellular roles in DAergic neurons and plays a critical role in DA signaling (54). Chronically administered drugs of abuse alter this intracellular cascade (53, 55). Genetically altered components of this system using modified mouse strains or other strategies can influence the behavioral effects of drugs (32). By extension, genetic differences in this system in humans strongly influence how an individual responds to drugs of abuse.

DOPAMINE NEUROTRANSMISSION AND DRUG ABUSE

Drug addiction is a general term encompassing the inability to cease drug-seeking and taking, possible incremental increases in drug intake or tolerance to the drugs pleasurable effects and physiological or psychological dependence. This drug intake continues despite deteriorating physical and mental health and social footing. Elicitation of a withdrawal syndrome involving physiological and/or psychological components upon drug discontinuation also signals drug dependence. Other important pharmacological aspects of drugs of abuse include cross-tolerance or tolerance to one substance that develops also to another substance usually in the same drug class. Similarly, cross-sensitization occurs when sensitization to one substance develops to a different drug also usually in the same class. Psychostimulants readily induce sensitization that is linked to DA and other neurotransmitters such as norepinephrine (NE) (56,57). Sensitization is considered key in the development of drug dependence (58), can be demonstrated in humans (59) and is linked to craving associated with unconditioned and conditioned drug effects (58) and relapse (60).

Data suggest that DA is associated with ‘euphoria’ elicited by drugs of abuse. DA is also associated with conditioning; it increases the ‘salience’ or attractiveness of external stimuli associated with drug procurement and intake (40). Similar to rodents (33), humans willingly self-administer psychostimulants under controlled conditions (61-63) that activate reward circuitry that is linked to drug-induced euphoria (61,64,65). Human imaging studies link DAT and D2 receptor occupancy with cocaine and amphetamine-induced euphoria (66,67). D1 (68) and D2 receptor antagonism (69,70) or altering DA metabolism (71) blocks the pleasurable effects of these drugs to some extent.

COCAINE ADDICTION AND ITS PHARMACOTHERAPY

Cocaine addiction is a persistent problem in the United States. The Office of National Drug Control Policy estimates that approximately 3 million individuals chronically use cocaine and years of research and drug development has yielded no indicated treatments (15,16). Cocaine blocks the re-uptake of a number of neurotransmitters including DA, NE and serotonin (5HT) (72). Yet, DA focused pharmacotherapies including DA antagonists as blocking agents, or direct DA agonists such as cabergoline (73) and bromocriptine (74) have shown limited success (15,16,74,75). However, indirect actions on DA through other neurotransmitters like GABA, such as baclofen (76) and tiagabine (77) show promise. Metabolically altering DA levels (and

blocking NE) through enzymatic inhibition may show the best efficacy for the treatment of cocaine addiction (78,79). Enzymes involved in the production of DA (80) as well as those involved in cocaine metabolism are significantly affected by genetics (81). Most intriguing are recently identified polymorphisms that alter subjective responses to psychostimulants (34, 35). Genetic polymorphisms that are involved in coding DA-related proteins involved in its regulation may guide individualized pharmacotherapy for cocaine addiction. One example discussed below is the DβH inhibitor disulfiram.

COCAINE ADDICTION: DISULFIRAM PHARMACOTHERAPY

Disulfiram (DS) presumably treats alcohol dependence by inhibiting the enzyme aldehyde dehydrogenase leading to increased plasma levels of acetaldehyde upon drinking alcohol, a byproduct of alcohol metabolism that is aversive (82). DS also chelates copper (83) in turn, inhibiting the copper-containing glycoprotein enzyme DβH that catalyzes the conversion of DA to NE in peripheral and central NE-containing neurons (84). DβH inhibition leads to decreases in peripheral and central NE and increases in DA (85,86). In humans, DS also inhibits plasma and microsomal carboxylesterases and plasma cholinesterase (87,88) that inactivate cocaine systemically thereby increasing blood levels (88). This effect likely contributes to DS's efficacy in treating cocaine addiction (89,90).

Controlled clinical trials support the efficacy of DS for cocaine dependence. DS reduces self-reported cocaine use and positive cocaine urine toxicologies in primary cocaine addicts, alcoholics and opiate dependent subjects who also abuse cocaine, and addicts maintained on methadone or buprenorphine. (91-95). DS's pharmacological effect is not specifically related to alcohol use (90). A meta-analysis of randomized controlled studies on the effectiveness of DS shows highly significant efficacy ($P < 0.001$). More recent studies also support DS as a significant treatment in primary cocaine abusers (79) and those with co-dependence (91, 93-96). Carroll et al. conducted a 12-week study and demonstrated that DS with psychotherapy decreased cocaine and alcohol use (91). A one-year follow-up analysis showed DS significantly reduced cocaine, but not alcohol use, suggesting the effect was specific (97). This result for cocaine was confirmed and extended by a more extensive study (79).

Early studies with DS alone showed that massive doses (up to 3 gm loading dose, and up to 1 gm/day for maintenance) induce paranoid psychosis in some patients (98). More recent studies of DS with cocaine showed that DS increases the aversive effects of cocaine such as nervousness that many cocaine abusers describe as "paranoia" (78). A subpopulation of cocaine addicts have a greater susceptibility to developing cocaine-induced paranoia, a characteristic that is genetically mediated (99). Although DS blocks enzymes that metabolize cocaine in the periphery, subjective measures of cocaine craving, 'high' or 'rush' associated with IV administered cocaine is reduced with DS treatment (78,95,100). This suggests that DS's therapeutic effects may more likely be due to its ability to inhibit DβH (increasing DA levels and decreasing NE) rather than just its pharmacodynamic effects (increasing systemic levels of cocaine).

When DβH levels are low, DA is increased whereas NE is decreased. Mice that lack DβH show increased DA in the PFC and decreased NE. Treatment with disulfiram further increases DA in this region (85). Cocaine potently blocks DA reuptake increasing synaptic levels of the neurotransmitter as does DS via DβH inhibition. Thus, its reasonable to conclude that cocaine/DS combination treatment results in supra-physiological increases in DA. This effect may contribute to the aversive characteristics of the drug as supported by human (88) and rodent studies (57,86,101). Under controlled laboratory conditions, Cubells et al. showed cocaine and DS combinations induce intense dysphoric reactions including psychotic symptoms in patients (102) but only in certain individuals suggesting that this effect was due to genetic factors

(99). Taken together, evidence supports that DS affects various behavioral effects of cocaine including blunting euphoria or 'high', neutralizing craving, or intensifying the dysphoric aspects of cocaine.

FUNCTIONAL SNP C-1021T AND DISULFIRAM ACTION

D*β*H is a synaptic vesicular enzyme that uses copper as a cofactor and oxygen and ascorbate as co-substrates (103). The enzyme converts DA into NE (104) and is co-released with catecholamines. Individuals genetically deficient in D*β*H usually perish at birth but those that have less severe forms exhibit physiological abnormalities namely, postural tachycardic syndrome or generalized autonomic failure because of lack of sympathetic tone (105-107). D*β*H is stable in plasma, correlates with cerebrospinal fluid (CSF) levels (108,109), and is age-dependent (110). Based on twin and family studies, plasma levels are variable between unrelated individuals (111-113). These genetically driven differences are likely due to polymorphisms in close proximity to the D*β*H gene. Studies link the C-1021T (-1021C>T) SNP to differences in circulating D*β*H levels (102,114-116) The SNP C-1021T is positioned ~1 kb upstream from the initiation codon of the D*β*H gene (116). Several studies support the notion that the C-1021T SNP is a functional polymorphism that gives rise to altered transcription and decreased plasma levels of D*β*H (116-119) but other SNPs may also play a role (80,120-122).

Decreased D*β*H attributed to C-1021T is found in diverse populations (European Americans, African Americans, Eastern Indian and Japanese) accounting for up to 52% of overall variation (116,118,119,123). Those individuals that are T allele homozygous have the lowest levels of plasma D*β*H activity (106,116,118,119,123). Differences in D*β*H enzyme levels or activity is linked with a number of psychiatric disorders including schizophrenia (114,124), psychotic depression (125), nicotine addiction (126), attention deficit hyperactivity disorder (ADHD) (127), post-traumatic stress disorder (128), conduct disorder (129-133), and neurological diseases involving DA neurotransmission such as Parkinson's Disease (80,134). The DA metabolite, homovanillic acid (HVA) found in CSF fluid is an indirect measure of monoamine concentration in the brain and is correlated with D*β*H C-1021T SNP genotype (135).

That C-1021T may be a functional polymorphism leading to decreased basal D*β*H levels has pharmacogenetic significance for treatment of cocaine dependence with DS. In individuals with already low levels of D*β*H enzyme, DS would be more effective in increasing DA and decreasing NE (e.g. heterozygous and more so for subjects homozygous for the T allele). Data from D*β*H deficient mice support this notion in that basal levels of DA in either +/- or -/- homozygous are increased two and five times respectively. DA:NE ratio is significantly reduced (approximately 35%) and DS pretreatment decreases NE and increases DA in wildtype and +/- mice (85). An imbalance in DA:NE in the PFC may underlie increased cocaine-induced paranoia in individuals with low levels of D*β*H attributed to the C-1021T SNP (80). This theory posits that DA:NE ratios may be elevated at baseline in those homozygous for the T allele. Cocaine, which potently increases DA levels, may lead to supra-physiological levels above that of cocaine alone contributing to cocaine-induced paranoia and psychosis. Consistent with this notion, controlled human experiments utilizing a 'binge' type cocaine self-administration paradigm show that subjects homozygous for the T allele ('very low-activity') in the D*β*H gene exhibit greater cocaine-induced paranoia compared to CT or CC genotypes (136,137). Moreover, cocaine abusers that experience cocaine-induced paranoia (that is extremely aversive) are more prone to develop psychosis and to seek immediate medical treatment (138,139). Preclinical studies in rats (101) and with genetically deficient D*β*H mice support this interpretation. Indeed, decreasing D*β*H through DS treatments or via genetic manipulation enhances the behavioral effects of cocaine and increases anxiety associated with the drug (57,86). Specifically, cocaine aversion is enhanced in D*β*H deficient mice and cocaine-induced

anxiety eliminated (57); the later effect appears to be mediated through beta-adrenergic receptors. In fact, DβH inhibition with DS facilitates cocaine-induced locomotor sensitization that may reflect enhanced aversiveness of the drug (101).

Taken together, SNP mapping profiles aimed at detecting DβH genotype may help predict whether an individual will respond well to DS treatment for cocaine dependence. That is, DS efficacy may be affected by an individual's genotype. Individuals harboring the DβH C-1021T SNP TT allele likely would respond better to DS treatments and need less of a dose whereas CT allelic carriers would need an intermediate dose and those with the CC allele may need increased concentrations for maximum therapeutic effectiveness. Evidence to date indicates that DS appears to be a good example of a pharmacogenetic treatment for drug abuse. Future studies are needed to clarify the mechanisms involved, and the contributions of other SNPs implicated in altering DβH levels that may affect treatment outcome.

DOPAMINE RECEPTOR D2 (DRD2)

Literature strongly supports D2 receptor involvement in the reinforcing effects of drugs of abuse. Imaging studies show significantly reduced levels of these receptors in alcoholics (140), cocaine (141), methamphetamine (142), and heroin abusers (143). D2 receptors are also related to drug-induced euphoria (65,144) and drug craving (145,146). Individuals with a positive family history of alcoholism—a predisposing factor to developing the disease—that have higher D2 receptor levels, are protected from developing drug dependence (147). Intriguingly, positron emission tomography (PET) imaging studies in drug näive rats show that low D2 receptors in the ventral striatum (which includes the NAc) predicts impulsivity and greater drug self-administration behavior (148). Predetermined rat phenotypes that readily self-administer drugs of abuse suggests genetic factors are involved (31,149). Inbred rat strains that have a proclivity to self-administer drugs of abuse across classes, have low D2 receptor density (149-151) and altered responses to DAergic agents (33). Similarly, genetic ablation of the D2 receptor in mice significantly decreases drug reward and responsivity (32,152,153). Accordingly, deficits in D2 receptors in some human drug abusers persist even after pro-longed periods of abstinence suggesting that these altered levels were not solely drug-induced (154). These data suggest an important role for genetic factors that affect D2 receptor availability and may predict inter-individual responses to drugs of abuse. Pharmacogenetic medications aimed at increasing D2 levels in those individuals genetically predetermined for low levels may prove beneficial.

DOPAMINE TRANSPORTER (DAT) *SLC6A3* GENE

The DAT is encoded by the *SLC6A3* gene (155) and sequesters DA back into the presynaptic neuron (see Figure 1) to modulate DAergic tone (48,49). Cocaine strongly inhibits DAT that is related to its reinforcing effects (156,157). Similarly, other psychostimulants, such as amphetamine and methamphetamine, have action at the DAT enhancing DA neurotransmitter release into the extracellular space potently increasing levels (158-160). Mice genetically deficient in DAT have altered responses to cocaine and amphetamine (161). The cocaine euphoria, or 'high' associated with self-administering the drug is correlated with DAT occupancy in humans (66). Thus, genetic alteration in DAT could contribute to altered sensitivity to cocaine in humans.

SLC6A3 comprises 15 exons spanning 60 kb on chromosome 5p15.32. The 3′-untranslated region (UTR) DAT1 polymorphism is a 40 bp VNTR with repeat copy numbers between 3-13 times with the 9 and 10-repeat allele being the most frequently found in the population (162-164). Unique to this polymorphism is that it is located in the untranslated region of the DAT1 gene but has been linked to disease phenotypes involving DA dysregulation. This suggests that it may be in linkage disequilibrium with another mutation that influences either

gene expression or functional aspects of the transporter. Preclinical studies suggest that this VNTR alters levels of gene expression, yet it is unknown precisely at what level (165-167).

DAT VNTR AND THERAPEUTIC RESPONSE TO METHYLPHENIDATE: ADHD MODEL

ADHD is a common disorder of childhood and adolescence associated with persistent impairment in academic and social spheres (168,169). Imaging studies generally show dysregulated DA-rich brain structures, altered presynaptic DA storage and abnormal DAT striatal density (170-175). Individuals with ADHD have a high rate of comorbid psychiatric illness with substance abuse occurring in 1 in 5 patients (168,176). Methylphenidate (and its various formulations) is the drug of choice for the treatment of ADHD and binds to the DAT similar to cocaine (39,66,177).

Some studies (178-181) but not all (166,182,183) indicate that the VNTR polymorphism of the DAT1 is a risk factor for psychiatric diseases associated with drug abuse such as ADHD. Haplotype is a combination of alleles at two or more closely linked gene loci on the same chromosome. VNTR polymorphisms located in intron 8 and the other 3′ untranslated region (3′-UTR) of the gene and the 10-repeat 3′ UTR alleles together appear as a common DAT1 haplotype (10/3) (181). Intriguing data from Bellgrove et al. show in normal developing healthy children, the DAT1 genotype—in particular the 10- and 3-repeat allele markers-influences attentional spatial bias and neglect displayed as inattention for left-sided stimuli, characteristics that could be related to the ADHD phenotype (184). Whether this combination haplotype confers risk, or alters pharmacological interventions for cocaine addiction is unknown. One large study showed that alleles of *SLC6A3* polymorphism 30 bp VNTR in intron 8 in patients addicted to cocaine and showed compromised function in in vitro reporter assays (185). Replication of this study in different subject populations is warranted.

Some studies show that ADHD individuals with the 10/10 genotype of the DAT1 VNTR show poor response to methylphenidate on clinical and physiological measures (186-191) whereas others have shown no significant response (192,193) or better response (191,194,195) to methylphenidate. Although far from conclusive, VNTR polymorphisms in the DAT1 gene confer clinically relevant alterations that may affect response to methylphenidate, a possible treatment for cocaine addiction.

Methylphenidate treatment is associated with significantly greater frequency of cocaine-free urines compared to placebo controls in cocaine dependent individuals with ADHD (196). Methylphenidate also has been shown to block some of the subjective effects of cocaine and reduce free choice of cocaine over a monetary reward (197). Methylphenidate's therapeutic action is unknown but likely involves increasing neurotransmission in the orbitofrontal cortex secondary to elevated DA in thalamic brain regions (39). Increased neurotransmission in the orbitofrontal cortex may contribute toward reversing the well-demonstrated finding of hypo-frontality in chronic cocaine dependent subjects (198). Restoring DAergic inhibitory influence from the prefrontal cortex on structures involved in affective drive (199) and executive functioning (200) may underlie normalizing compulsive drug-seeking behaviors.

Properly assessed genetically driven functional changes in the DAT could help determine which patient would benefit most from methylphenidate for cocaine addiction (32). Imaging studies indicate that the 9/9 and 9/10 genotypes are associated with differences in DAT availability *in vivo*. Some imaging groups find decreased DAT availability of 9/10 allele vs. 10/10 carriers (201) or no difference (202). However, our early collaborating studies using single photon emission tomography (SPECT) and the [123I] beta-CIT ligand highly selective D2 (and D3) receptor ligand noted a 13% *increase* in striatal binding in the 9/10 repeat

heterozygotes compared with the 10 repeat homozygotes in normal non-diseased subjects (203). A more recent study confirmed these findings using the same SPECT ligand in normal subjects. *SLC6A3* 9 repeat carriers (in this study combined 9/9 and 9/10 genotypes) have significantly higher striatal DAT availability compared to 10 repeat homozygotes (204) suggesting that the *SLC6A3* 9 repeat genotype leads to increased DAT availability in striatum. Although *in vitro* studies give conflicting conclusions as to the extent to which variants regulate transcriptional activity or number of DAT proteins (165,166,202,205), it is likely that altered DAT levels contribute to inter-individual differences in the ability of the transporter to clear DA from the synaptic space. Supra-physiological levels of orbitofrontal DA presumably contribute to psychotic symptoms such as paranoid ideation (206). Increased DA levels in this area are also linked to the euphoric effects of cocaine (177,200). Thus, more DAT in the 9 repeat carriers would presumably sequester greater amounts of synaptic DA in turn reducing the initial pleasurable effects of drugs and perhaps 'protecting' the individual from developing drug addiction. This interpretation is consistent with the finding that euphoric effects of amphetamine are significantly decreased (35) in the 9 repeat carriers as is therapeutic response to methylphenidate (178,195).

Taken together, conflicting results demonstrating altered DAT1 concentrations and/or function are difficult to interpret within the context of methylphenidate treatment for cocaine addiction. Evidence suggests however, that since the VNTR is in an untranslated region and-presently unknown to produce any functional protein-it may be a marker associated with another mutation in linkage disequilibrium that influences either gene expression or functional aspects of the transporter. The presence of ADHD in cocaine dependent subjects in tandem with genotype are important factors to consider in predicting therapeutic response for methylphenidate for cocaine.

AMPHETAMINE: MECHANISMS OF ACTION AND PHAMACOGENETICS

Amphetamine was first used commercially as an over-the-counter inhaler for nasal congestion and asthma (160,207). Today, amphetamine is used medically for ADHD, narcolepsy with off label use for chronic fatigue syndrome, and adjunct therapy for anhedonia associated with refractory depression. Amphetamine and its derivatives, such as methamphetamine, are widely abused illicit drugs second only to cannabis.

Early studies show that responses vary greatly from one individual to another in response to the same dose of amphetamine (208-210). This heterogeneity of response may be due to a number of factors such as expectancies of the drug (211), psychiatric disease or personality type (212,213), or gender differences (214). Yet, considerable evidence shows that individual variability in drug response is due to genetics (160). For example, polymorphisms DAT 3′UTR VNTR (35), COMT val158met (215), SLC6A2 NET intronic 36001 C/C (216), 5-HT transporter gene-linked polymorphic region and Intron 2 VNTR (217), adenosine receptor A2a 1976 C/T and 2592 C/Tins (218), casein kinase 1 epsilon (219) and BDNF G196A val66met (220) have all been implicated in altering the subjective effects of amphetamine.

Amphetamine's primary effects are mediated by action on the DAT. Similar to cocaine and methamphetamine, amphetamine has strong effects on the DAT, reversing the transporter enhancing extraneuronal DA concentrations (158). As mentioned, the *SLC6A3* 3′-UTR DAT1 polymorphism VNTR, frequently found in the population (162-164), affects gene expression (221), results in altered central DAT levels (166,201-204), and impacts subjective and therapeutic efficacy of the ADHD drug methylphenidate (178,195). Similarly, the DAT gene is crucial to individual variability in response to amphetamine (35). Subjects with the 9/9 DAT1 variant report ***no*** euphoria, anxiety or "feel drug" responses to increasing doses of amphetamine compared to those with the 9/10 or 10/10 alleles. Homozygous 9/9 repeat allele carriers also

have significant decreases in peripheral physiological measures, such as diastolic blood pressure. These data are consistent with studies showing that individuals who have the 9/9 repeat genotype do not respond to the ADHD medication methylphenidate (178,195).

Initial pleasurable experiences with drugs of abuse predict future use and dependence (222, 223). By extension, subjects with the 9/9 allele experience less positive subjective effects of psychostimulants, in this case amphetamine, and may be "protected" from developing future psychostimulant abuse. Studies in genetically diverse inbred strains Lewis and Fischer 344 rats support this conjecture. Lewis rats (vs. F344 rats) have innate predisposition to self-administer a wide variety of drugs of abuse and have low baseline DAT levels and function (224). Haile et al. (2005) recently showed that the potent and selective DAT inhibitor RTI 336 decreases cocaine-induced activity and self-administration in Lewis but not F344 rats (225). That a highly selective DAT inhibitor was more effective in decreasing cocaine's behavioral effects in a genotype known to have decreased DAT levels supports this as a possible therapeutic target. Future studies determining if the *SLC6A3* 3′-UTR DAT1 VNTR polymorphism is a useful phamacogenetic marker for medications to treat amphetamine and cocaine abuse in humans are warranted.

METHAMPHETAMINE

Methamphetamine (METH) is a potent and highly addictive psychostimulant (160). METH efficiently penetrates the CNS (226) evoking the release of high concentrations of monoamines, in particular DA, through multiple mechanisms (158). The half-life of cocaine is 90 minutes whereas METH is upwards of 10 hours (227). Abusers tend to self-administer the drug in "binges" or "runs" lasting 1-3 days or more followed by abstinence then repeated abuse. Because of METH's lengthy half-life, 'binge' administration results in increasing concentrations of the drug within the system that can be toxic particularly because minimal tolerance occurs to its peripheral and central effects (228,229).

Acute administration of METH produces powerful sympathetic nervous system stimulation. Euphoria, increased energy, heightened attentiveness, hypersexuality, and decreased anxiety are effects of METH intoxication (230). In contrast, depression, anhedonia, irritability, anxiety, fatigue, hypersomnia, poor concentration, intense craving and aggression are associated with METH withdrawal (231-233). Chronic METH ingestion frequently results in severe psychiatric disturbances or METH-induced "psychosis" that resembles schizophrenia (234-236). There are presently no FDA-approved medications indicated for METH addiction but a variety of compounds are being tested (237).

METHAMPHETAMINE'S EFFECTS ON NEUROCHEMISTRY AND BEHAVIOR

METH is similar to cocaine and amphetamine in that it has potent effects on the DAT that likely contribute to its addictive properties. METH greatly enhances DA concentration in reward circuitry, such as the NAC, 1000% over baseline (238) independent of neuron depolarization (239) redistributing cytosolic DA for quick release from the neuron (240). Redistribution of cytosolic DA may be due to METH's ability to inactivate vesicular monoamine transporter (VMAT2) in monaminergic neurons (241) that is normally responsible for repackaging, storage and re-release of neurotransmitter. METH-induced increases in massive amounts of synaptic DA is auto-oxidized into highly reactive species that inactivates and decreases DAT that further elevates synaptic DA levels (242-244) and neurotoxicity (120,245-247). DA selective receptor antagonists, DAT antagonists, and DA depletion block METH's effects on the DAT (248). Likewise, DA D1-like and D2-like antagonists also block METH-induced behavioral sensitization in rats (249,250). Clozapine, an atypical antipsychotic that blocks a number of receptors, including the D4 receptor subtype (251), antagonizes METH-induced behavioral activation as does a D4 selective antagonist (252). Clozapine

pretreatment also blocks METH-induced memory deficits in rodents (253). Neither the non-selective DA blocker haloperidol nor the combination DA D2/5HT blocker risperidone block the subjective effects of METH in humans (254).

Individuals with METH abuse histories have significant decreases in DAT binding in the caudate and putamen as measured with the PET radioligand [^{11}C]WIN-35,428 (255). Other PET studies confirm decreased DAT binding in these areas in current abusers (256), recently detoxified subjects (257), and in subjects drug-free for upwards of 11 months (142). Similar to what has been demonstrated in alcoholics (140), cocaine (141), and heroin (143) abusers, D2 receptor levels are lower in the caudate and putamen of METH abusers, as measured by PET [^{11}C]raclopride (142)(but see (257)).

Research has focused on polymorphisms involving the DAergic system that relates to METH-induced psychosis and vulnerability. The 7-repeat (exon III) DRD4 polymorphism and the functional polymorphism COMT Val158Met are two examples (258-261). Substantive evidence supports an association with the met allele of the COMT enzyme with METH-induced psychosis (262) and as a risk factor for developing prolonged METH-induced psychosis (263). METH-psychosis is associated with proteins linked to DA neurotransmission such as C-kinase-1 (PICK1) that is related to DAT membrane localization and securing a stable protein complex within the membrane (264). Others include the functional polymorphism of glutathione S-transferase involved in oxidative stress protection that results in markedly reduced enzyme (30%) levels possibly potentiating METH's deleterious effects (265,266). Organic cation transporter 3 (267), beta-arrestin 2 gene (268), and newly identified SNPs of OPRM1 (269,270), but not the delta opioid receptor (OPRD1) (271), have also been linked to METH-induced psychosis.

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor implicated in a number of neurological processes such as cell survival, proliferation, synaptic growth through development, and hippocampal changes associated with learning and conditioned drug reward (272-275). Interestingly, plasma BDNF levels are significantly higher in abstinent METH abusers compared to controls (183) and in multiple substance abusers with schizophrenia (276). Recent association studies have linked an increased incidence of the purported functional BDNF gene polymorphism val66met (277) and substance abuse in males (278). This mutation appears to affect declarative memory in humans (279). Increased incidence of the val66met polymorphism in substance abusers is partly supported by another study (280). It is unknown however, whether the val66met polymorphism alters any of the subjective effects of METH or rather, may be a viable pharmacogenetic target.

Taken together, there has been much progress made in defining polymorphism that may confer susceptibility to abuse and developing psychosis from METH abuse. From a pharmacogenetics perspective, studies have yet to find a target that would improve pharmacotherapeutic decision-making in the setting of variability in response to a drug therapy for this drug of abuse.

CONCLUSIONS

Identifying gene-targets that will improve clinical decision making within the context of variability in response to drug therapy is the principle challenge of pharmacogenetics. Psychiatric pharmacogenetic studies have identified genes implicated in altered responses to psychostimulants and have identified targets for maximizing pharmacotherapeutic response. Studies presented here briefly highlighted therapeutics for drug dependence currently being used but focused mainly on maximizing therapeutic response based on individual's genetic profile. For example, cocaine pharmacotherapy is influenced by C-1021T SNP of the DβH gene that alters enzyme levels. Disulfiram's action on this enzyme and DAT gene variable

number tandem repeats of the *SLC6A3* gene affects treatment response to methylphenidate. DAD4 receptor 77-repeat (exon III) polymorphism may alterclozapine action for the treatment of METH-induced psychosis. Further, the purported functional polymorphism of the BDNF gene val66met may offer a pharmacogenetic target for METH addiction. Val158met may alter COMT enzyme levels and is associated with amphetamine and METH use. Presumed genetically predetermined decreases in DRD2 levels in chronic drug abusers offers another possible pharmacotherapeutic target (see Figure 2).

Individualized treatments based on the presence of SNPs or other gene variants that alter a particular target protein's function but enhance response to a medication is key. Better-defined contributions of genes already associated with drugs of abuse and how they may alter the subjective effects that contribute to pathological compulsive drug seeking is under way. Future studies should consider gene variants that affect pharmacodynamic, pharmacokinetic and possibly epigenetic factors that could contribute to a positive clinical outcome and response to a particular medication. Information from imaging studies coupled with carefully defined candidate gene variants and their function will also help clarify contributions of candidate genes to phenotype and possibly predict responses to psychostimulants and to medication.

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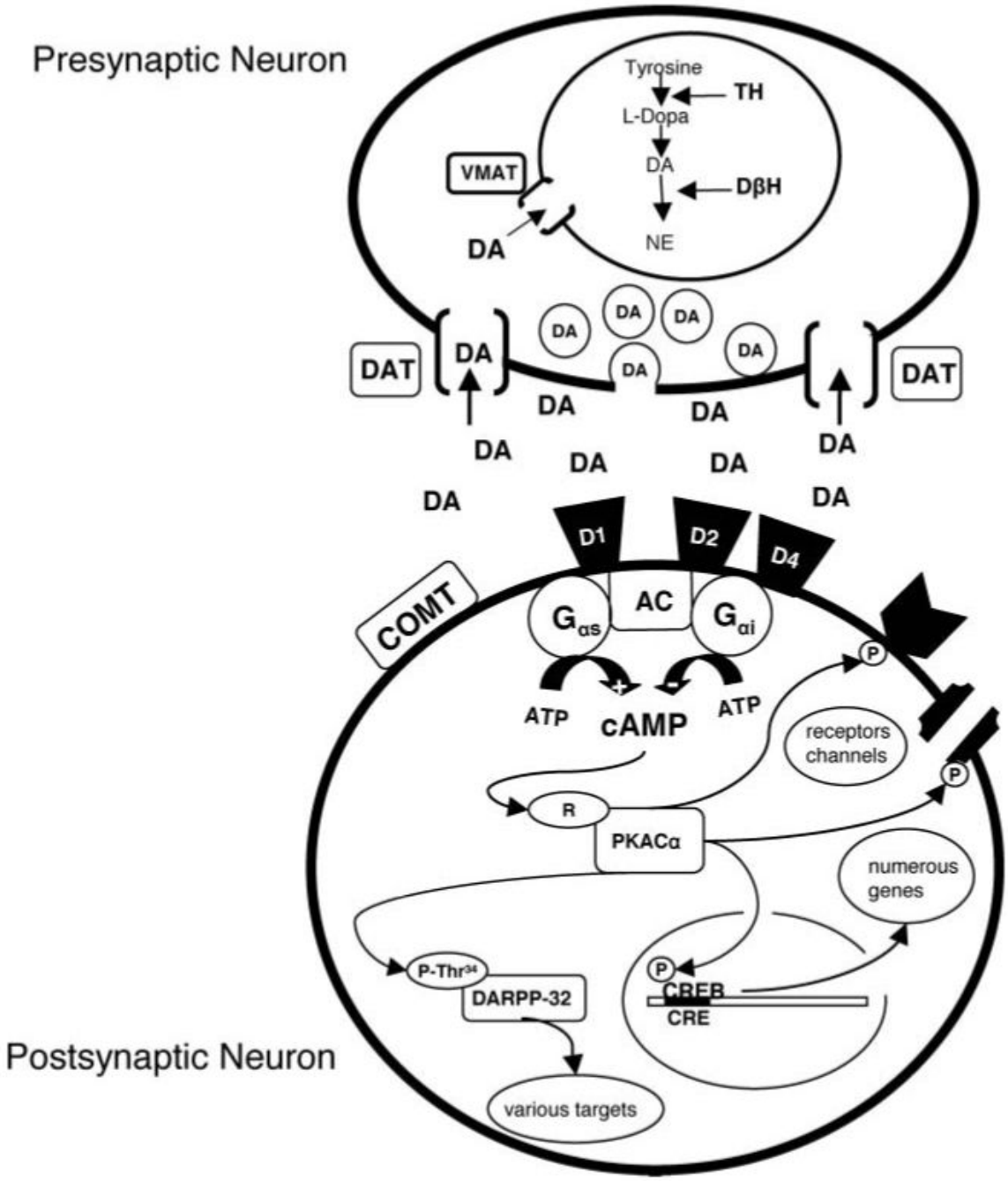

FIG. 1.

Hypothetical schematic of a DAergic synapse. Presynaptic neuron contains DA precursors leading to vesicular DA fusing with the presynaptic membrane and being released into the synaptic cleft. DA then stimulates DAergic receptors on the postsynaptic cell. DA is inactivated by being sequestered back into the presynaptic neuron by the DA transporter (DAT). DA may also be metabolized extra-synaptically by catechol-O-methyl transferase (COMT). DA present in the cytosol is taken up by the vesicular transporter (VMAT) for degradation and repackaging. Tyrosine hydroxylase is the rate-limiting enzyme in DA synthesis. Dopamine beta-hydroxylase (D*β*H) is responsible for the formation of norepinephrine (NE). Intracellular mechanisms associated with the cAMP-PKA-CREB pathway through DA D1-like and D2-like receptors

are represented in the postsynaptic neuron. D1 stimulates through G*α*s whereas D2 receptor activation inhibits cAMP levels via adenylate cyclase (AC) through G*α*i G-proteins. cAMP enhances the dissociation of the regulatory subunit of proteins kinase A (PKA) from the catalytic subunit (C*α*) causing activation. PKA-C*α* may translocate to the nucleus where it phosphorylates cAMP-response element binding protein (CREB) that leads to cAMP response element (CRE)-mediated gene expression. PKA-C*α* may phosphorylate other receptors or channels as well. This kinase also phosphorylates dopamine-and cAMP-regulated-phosphoprotein 32 kDa (DARPP-32) at position Thr34, that then leads to regulation of other intracellular proteins and effects on the neuron.

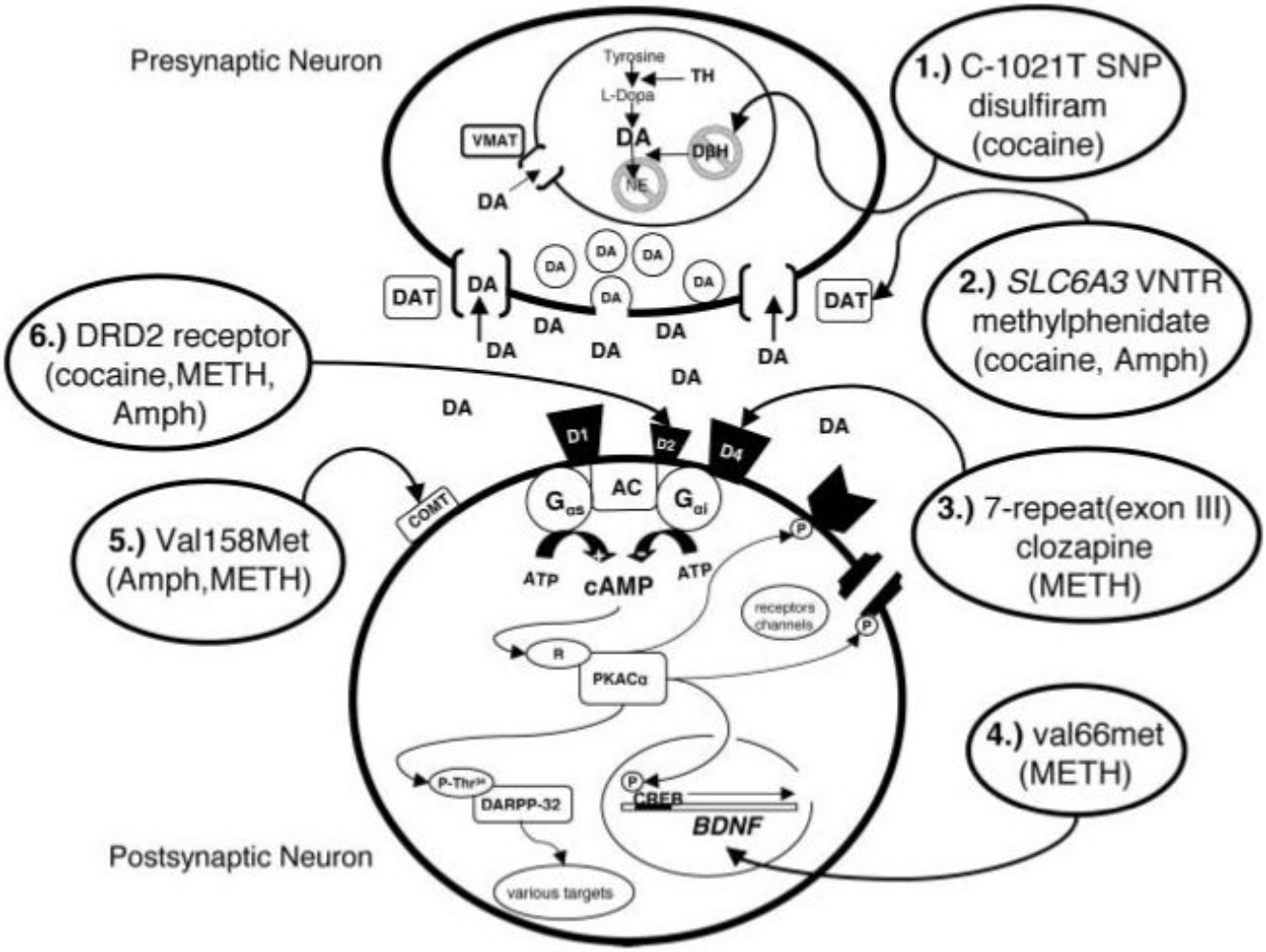

FIG. 2.

Hypothetical schematic of a DAergic synapse representing various polymorphisms affecting proteins involved in psychostimulant action or altering response to medications for psychostimulant addiction. Cocaine pharmacotherapy is influenced by C-1021T SNP (1) of the D*β*H gene that alters enzyme levels and disulfiram's action on this enzyme. DAT gene variable number tandem repeats of the SLC6A3 (2) affects treatment response to methylphenidate and possibly cocaine and amphetamine (AMPH). DAD4 receptor 7-repeat (exon III) polymorphism (3) may alter clozapine action for the treatment of methamphetamine (METH)-induced psychosis. The purported functional polymorphism of the BDNF gene val66met (4) may offer a pharmacogenetic target for METH addiction. Val158met (5) may alter COMT enzyme levels and is associated with AMPH and METH use. Genetically predetermined decreases in DRD2 receptors (6) in chronic drug abusers across classes offers a possible pharmacotherapeutic target.