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Pharmacotherapeutics directed at deficiencies associated with cocaine dependence: Focus on dopamine, norepinephrine and glutamate

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Abstract

Much effort has been devoted to research focused on pharmacotherapies for cocaine dependence yet there are no FDA-approved medications for this brain disease. Preclinical models have been essential to defining the central and peripheral effects produced by cocaine. Recent evidence suggests that cocaine exerts its reinforcing effects by acting on multiple neurotransmitter systems within mesocorticolimbic circuitry. Imaging studies in cocaine-dependent individuals have identified deficiencies in dopaminergic signaling primarily localized to corticolimbic areas. In addition to dysregulated striatal dopamine, norepinephrine and glutamate are also altered in cocaine dependence. In this review, we present these brain abnormalities as therapeutic targets for the treatment of cocaine dependence. We then survey promising medications that exert their therapeutic effects by presumably ameliorating these brain deficiencies. Correcting neurochemical deficits in cocaine-dependent individuals improves memory and impulse control, and reduces drug craving that may decrease cocaine use. We hypothesize that using medications aimed at reversing known neurochemical imbalances is likely to be more productive than current approaches. This view is also consistent with treatment paradigms used in neuropsychiatry and general medicine.

Keywords

Addiction; Cocaine dependence; Medication development; Dopamine; Glutamate; Norepinephrine; Neurotransmission; Neuroplasticity; Behavioral pharmacology

1. Introduction

The development of pharmacotherapies for the treatment of cocaine dependence has been a high priority in addiction research for more than two decades, yet no medication has been approved by the Food and Drug Administration (FDA) in the USA or by similar agencies in other countries for this disease (Rawson et al., 2004; Vocci & Montoya, 2009). The absence of efficacious treatments remains a significant problem since, for example, the National Survey on Drug Use and Health statistics from 2010 shows that approximately 1.5 million individuals in the USA were current cocaine users. Moreover, data from the Treatment Episode Data Set for 1998–2008 suggested that 17% of all patients who entered drug treatment programs in the USA did so for the treatment of stimulant addiction (SAMHSA, 2010b).

Cocaine use is associated with significant medical and psychiatric morbidity. The Drug Abuse Warning Network, an organization in the USA that monitors substance abuse-related emergency room visits, estimated that over 500,000 drug misuse or abuse visits were the result of recent cocaine exposure. Indeed, cocaine accounted for a majority of drug-related emergency room visits in the USA (SAMHSA, 2010a). Among the many adverse medical consequences of chronic cocaine use, cardiovascular events appear prominent (Diercks et al., 2008). Disease transmission through intravenous use and medical debility secondary to major cardiovascular events, such as stroke and myocardial infarction, continues to stress care management resources (Degenhardt et al., 2010). Evidence-based ranking scores that objectively measure drug-harmfulness indicate that cocaine is second only to heroin among illegal drugs (Nutt et al., 2007).

Much progress regarding the neuroscience of cocaine dependence has been achieved through basic biochemical research and the use of animal models of human drug dependence. In addition, data acquired in human laboratory studies and neuroimaging have been pivotal to advancing our understanding of cocaine's powerful reinforcing effects. Indeed, this understanding has provided important information regarding the development of promising pharmacotherapies for cocaine dependence contained in this review.

1.1. Pharmacology and pharmacokinetics of cocaine

Cocaine exists in primarily two forms: free base and cocaine hydrochloride salt. The salt form is usually a white powder whereas its base form is typically white to light brown depending upon impurities. Cocaine hydrochloride is water soluble thus can be taken intranasally or dissolved in a water vehicle and administered intravenously. The free-base crystalline form of cocaine or "crack" is insoluble in water and is usually volatilized or "smoked". The term "crack" is derived from the audible crackling noise produced when this form is heated as it is smoked. Street forms of cocaine may contain adulterants such as sugar, and anesthetics like lidocaine and benzocaine (Fucci & De Giovanni, 1998) (McKinney et al., 1992) and other adulterants (Evrard et al., 2010) (Brunt et al., 2009). Of particular concern is the recent finding that nearly 70% of seized cocaine entering the USA contains detectable amounts of the agranulocytosis-inducing, anti-helminthic drug, levamisole. Although most samples contain only trace amounts, this adulterant has been responsible for numerous hospitalizations and deaths (CDC, 2009; Czuchlewski et al., 2010; Buchanan et al., 2011). Why this drug in particular is used to dilute illicit cocaine is an interesting and pressing question.

After ingestion, cocaine is metabolized by the liver and plasma cholinesterases into the inactive water soluble metabolites benzoylecgonine and ecgonine methyl ester. These are then excreted in the urine. Urinary metabolites represent approximately 90% of the original cocaine dose with a small percentage excreted as intact parent compound (Van Dyke et al., 1977; Jatlow, 1988). Hepatic N-demethylated cocaine yields a small amount of norcocaine, a pharmacologically active metabolite (Hawks et al., 1974) and other minor inactive metabolites (Kolbrich et al., 2006).

The speed at which cocaine enters the systemic circulation is dependent upon route of administration. Oral or intranasal administration produces slow increases in cocaine plasma concentrations whereas smoked or intravenous (IV) administration results in rapid delivery of cocaine to the brain. These differences explain why smoked or IV administration produce greater reinforcing effects compared to oral or intranasal cocaine. Rapid increases in plasma concentrations of cocaine are directly correlated to its physiological and subjective effects (Javaid et al., 1978; Newton et al., 2005). In fact, human imaging studies show that the quicker an addictive drug enters systemic circulation and crosses the blood brain barrier, the higher its abuse liability (Volkow et al., 2000; Fowler et al., 2008; Reed et al., 2009).

1.2. Mesocorticolimbic circuitry: an important cocaine substrate

Dopaminergic cell bodies in the ventral tegmental area (VTA) and their projections to the nucleus accumbens (NAc) and prefrontal cortex (PFC), and glutamate (GLU) projections from the PFC to both the VTA and NAc, generally define the fundamental circuitry of the mesocorticolimbic reward system. Other important brain structures associated with emotional memories and drug taking and dependence include the amygdala, hippocampus and hypothalamus (Everitt & Robbins, 2005; Rocha & Kalivas, 2010). Cocaine and other stimulants rapidly increase dopamine (DA) levels in the PFC and NAc and lesions of these brain areas alter cocaine's behavioral effects (Roberts & Koob, 1982; Pettit et al., 1984; Di Chiara & Imperato, 1988). Although other neurotransmitter systems are clearly involved, studies strongly support that activation of the mesocorticolimbic system is key to the reinforcing effects produced by cocaine in humans (Childress et al., 1999; Volkow et al., 2010).

A number of DA receptor subtypes are presently known. These include the D1-like (D1, D5) and D2-like (D2, D3, and D4) receptor families, which are classified according to their molecular and pharmacological characteristics. For example, activation of D1-like receptors increases cyclic adenosine 3', 5'-monophosphate (cAMP) through stimulation of adenylate cyclase via G_s stimulatory G-proteins whereas activation of D2-like receptors through G_i inhibitory G-proteins decreases cAMP. The formation of cAMP is dependent upon adenylate cyclase (AC) and degraded by phosphodiesterase enzymes in the cytoplasm. Increased cAMP participates in a variety of intracellular processes that involve kinases, including protein kinase A (PKA) and G-protein receptor kinase 3 (GRK3). PKA acts on enzymes, phosphorylates receptors and channels, and activates important transcription factors like cyclic adenosine monophosphate response-element binding protein (CREB) (Terwilliger et al., 1991; Carlezon et al., 2005; Dinieri et al., 2009). Cocaine alters this intracellular pathway and the expression of gene products dependent upon proper signaling. Some examples include brain-derived neurotrophic factor, cyclin-dependent kinase 5, nuclear factor kappa-B, GluR1 (AMPA glutamate receptor sub-type-1), among others, implicated in cocaine-induced neuroplasticity (Ang et al., 2001; Nestler, 2002; Le Foll et al., 2005; Tsai, 2007).

1.3. Behavioral pharmacology of cocaine in laboratory animal models

Animal models of human drug-dependence have been essential in determining the central pharmacological action and behavioral effects produced by cocaine. Cocaine induces a wide array of behavioral effects in laboratory animals that primarily depend upon the behavioral model being used. For instance, low to moderate doses of acutely administered cocaine stimulates locomotor activity (Wise & Bozarth, 1987) whereas high doses increase stereotyped behaviors (e.g., sniffing, chewing, rearing, etc.) that impede locomotion and other non-stereotypic behaviors (Barr et al., 1983). These behavioral effects can be enhanced (i.e., sensitized) with repeated drug dosing over time (Ellinwood & Balster, 1974; Wise & Bozarth, 1987; Robinson & Berridge, 1993).

One theory posits that drug craving in humans may be a type of sensitization. That is, when drug-dependent individuals take drugs within a specific context, exposure to that context can provoke a greater craving response (Stewart et al., 1984; Robinson & Berridge, 1993). It is likely that unconditioned and context-dependent conditioning effects of repeated cocaine exposure reflect different but interconnected neural circuits. In fact, neural circuits that mediate the development of locomotor sensitization to cocaine differ from those that contribute to its expression (Vanderschuren & Kalivas, 2000). Similarly, the development and expression of cocaine-induced place conditioning (a type of reward-mediated learning) likely reflect different neuropharmacological mechanisms than those engaged during

locomotor sensitization (Spiraki et al., 1982). It is difficult to relate preclinical studies of sensitization to clinical observations because, unlike studies using animals, humans are chronically exposed to many different drugs (e.g. nicotine, alcohol, caffeine) over many years.

Cocaine can modify behavior by acting as a cue or discriminative stimulus that can elicit specific learned behavioral responses (Colpaert et al., 1976; McKenna & Ho, 1980; Kleven et al., 1990; Katz et al., 1991; Broadbent et al., 1995). Cocaine administered via injection can, for example, signal the animal that pressing on a lever paired with cocaine will result in a food pellet, whereas pressing on a saline-paired lever will not. Studies using this behavioral paradigm demonstrate that the cocaine discriminative stimulus is pharmacologically specific and generalizes only to other compounds that have similar pharmacological actions such as DA releasers (e.g., amphetamine) or other DA reuptake inhibitors (Cook et al., 2002). In contrast, animals that learn to discriminate cocaine do not generalize to compounds with dissimilar pharmacological actions or to those in a different drug class (e.g., pentobarbital). The degree to which the discriminative stimulus effects of a compound generalize to a drug of abuse (such as cocaine) is thought to reflect the abuse liability of the compound (Solinas et al., 2006).

There is a good deal of concordance between the discriminative stimulus and subjective effects produced by drugs in humans (Kamien et al., 1993). Consistent with circuitry involved in mediating the reinforcing effects of cocaine, drugs that act on DA, norepinephrine (NE) and GLU systems significantly affect the discriminative stimulus of cocaine in laboratory animals and humans (Sinnott et al., 1999; Lee et al., 2005; Negus et al., 2007; Lile et al., 2010).

An extensive literature describes other techniques used in animals to test the behavioral effects of drugs of abuse (Lynch et al., 2010) that are also used in humans in a controlled laboratory setting (Comer et al., 2008). While results from animal experimental paradigms do not always correlate with similar experiments in humans (Angarita et al., 2010), it is clear that the self-administration paradigm offers a direct measure of a drug's reinforcing effects. Indeed, cocaine is readily self-administered by numerous animal species (Seevers & Schuster, 1967) suggesting that the drug self-administration behavioral paradigm would possess excellent face validity as an animal model of human drug addiction (Deroche-Gamonet et al., 2004; Vanderschuren & Everitt, 2004). For instance, like the dependent human performing particular "tasks", often within a particular environment, to procure drug, the laboratory animal is willing to work (e.g., lever-pressing in an operant chamber) to receive a drug reward (Caine & Koob, 1993; Comer et al., 2008). Drugs that increase the likelihood that the behavior preceding a drug infusion will occur again are said to serve as positive reinforcers or to be reinforcing (Pickens et al., 1968; Schuster & Thompson, 1969). Most psychoactive drugs self-administered by humans also serve as positive reinforcers in animals suggesting that the drug self-administration paradigm may also serve to predict abuse liability in humans and provide a laboratory means to assess possible pharmacotherapies for drug dependence (Collins et al., 1984; Comer et al., 2008).

Different drug self-administration paradigms attempt to model distinct aspects of addiction. For example, acquisition of drug self-administration (i.e., the time it takes for an animal to acquire the operant task and demonstrate consistent self-administration behaviors) is thought to model aspects of the vulnerability to develop addiction (Deminier et al., 1989). One way that drug "craving" or drug "seeking" can be modeled in rodents is by replacing a reliably self-administered drug with saline and assessing the latency to extinguish self-administration behavior or persistence thereof (Markou et al., 1993). Replacing the drug with saline normally extinguishes cocaine seeking that can be re-established with non-contingent

cocaine infusions (i.e. priming), conditioned cues and stress (Ahmed & Koob, 1997; Piazza & Le Moal, 1998; Erb et al., 2000). In general, this animal model of “relapse” appears to be somewhat applicable to humans (de Wit & Stewart, 1981; Markou et al., 1993; Yahyavi-Firouz-Abadi & See, 2009). For example, cocaine-dependent individuals often state that environmental cues that are associated with taking cocaine trigger intense craving and this is why they tend to relapse (Gawin & Kleber, 1986). Much research is needed, however, to establish the predictive validity of these relapse models as they apply to humans for the development of medications for cocaine dependence (Katz & Higgins, 2003).

2. Behavioral pharmacology of cocaine in humans

One of the most important goals of human laboratory research has been to develop a safe and efficacious pharmacotherapy for cocaine dependence. In spite of much scientific research, no FDA-approved medication is available to treat this debilitating disease. The lack of success thus far is likely because of cocaine’s complex central effects and potent reinforcing properties. Regardless the route of administration, humans dose-dependently self-administer cocaine under controlled laboratory conditions (Fischman et al., 1976; Muntaner et al., 1989; Foltin et al., 2003a, 2003b; Newton et al., 2005; Comer et al., 2008; Stoops et al., 2010). However, when given a choice, Foltin and Fischman found that cocaine-dependent volunteers preferred the smoking route over even IV, though the dose available undoubtedly affects this outcome (Foltin & Fischman, 1992). The reason smoked cocaine is preferred is intriguing and may be more related to the rapid and potent euphoric effects produced by “crack” cocaine. For example, in one pharmacokinetic study assessing cocaine-dependent volunteers rated the subjective effects of cumulative smoking doses (0, 25 and 50 mg) greater than that of IV cocaine (0, 16, 32 mg). Although both smoked and IV administered cocaine result in similar systemic concentrations, and produce equivalent effects on cardiovascular measures, volunteers rated the positive subjective effects for smoked cocaine to be greater than those produced by IV administration (Foltin & Fischman, 1991). Preference for the smoked route is most likely related to the rapidity at which this formulation enters arterial systemic circulation and enters the brain (15 s for smoked vs. 240 s for IV) (Evans et al., 1996).

Unlike sensitization to the behavioral effects of cocaine seen in laboratory animals, acute tolerance quickly develops to the cardiovascular and subjective effects produced by cocaine in humans (Foltin & Fischman, 1991; Ward et al., 1997a, 1997b; Foltin & Haney, 2004). Although far from conclusive, one longitudinal study documented that while cocaine users increased the amount of cocaine they consumed over years, cocaine’s positive subjective effects decreased while the negative effects increased (Reed et al., 2009). The neurochemical mechanisms that underlie tolerance to cocaine’s effects over many years of use are not clear. Recent evidence suggests that chronic cocaine renders the DA transporter (DAT) insensitive to its effects (Ferris et al., 2010). In contrast, amphetamine (AMPH) is a substrate for the DAT and AMPH maintains its potent effects on this transporter even after exposure to chronic cocaine (Ferris et al., 2010). AMPH’s ability to counter cocaine’s action at the DAT after chronic cocaine treatment suggests a viable pharmacotherapeutic target. Indeed, as will be described later, a growing pre-clinical and clinical literature repeatedly demonstrates that chronic, but not acute, treatment with AMPH and AMPH-like medications used to treat attention deficit hyperactivity disorder (ADHD) and refractory obesity in adolescents and adults may be efficacious for cocaine dependence (see Section 5).

2.1. Cocaine: effects on DA neurotransmission

Natural rewards and drugs of abuse including cocaine activate the mesocorticolimbic DA system (Di Chiara & Imperato, 1988; Wise & Rompre, 1989). While cocaine has numerous effects on physiology and neurochemistry of this system, the primary mechanism underlying

its potent reinforcing effects is by DA reuptake inhibition (Harris & Baldessarini, 1973). Clear evidence shows that cocaine's reinforcing properties are linked to its ability to increase synaptic DA by binding to the DAT (Ritz et al., 1987). Indeed, molecularly engineering the DAT to render it insensitive to cocaine abolishes its potent reinforcing effects (Thomsen et al., 2009). The DAT is inserted into the neuronal membrane and acts to translocate DA into the cell via a concentration gradient. Thus, by blocking the DAT, cocaine increases synaptic DA to supra-physiological levels (Pettit & Justice, 1989). DA may then be degraded by the enzyme monoamine oxidase. Acute exposure to cocaine increases DAT insertion into the membrane thus counteracting effects of cocaine (Glowinski & Iversen, 1966; Snyder & Coyle, 1969).

Several studies have unequivocally associated DA neurotransmission with self-reports of 'euphoria' or 'high' (more generally — the positive subjective effects) elicited by cocaine. Activation of reward-related brain circuitry in humans (e.g., NAc or ventral striatum, orbitofrontal cortex) is associated with stimulant-induced euphoria occupancy with cocaine-induced euphoria (Volkow et al., 1999). Interrupting DA neurotransmission using DA receptor antagonists partially attenuates the positive subjective effects of cocaine in humans (Sherer et al., 1989; Newton et al., 2001). Complete blockade of the positive subjective effects of stimulants is not achieved by selectively compromising DA and suggests other transmitter systems must be involved (Newton et al., 2001). Reanalysis of early experiments in animals and humans does indicate, for example, that NE plays a significant role (Weinshenker & Schroeder, 2007). Moreover, compounds that show promise for stimulant dependence alter NE neurotransmission through a number of mechanisms (Carroll et al., 1998, 2004; Baker et al., 2007; Mitchell et al., 2008; Sofuoglu et al., 2009; De La Garza et al., 2010).

Because one of cocaine's primary mechanisms of action is to increase synaptic DA levels, research has focused on identifying a therapeutic drug for cocaine dependence that blocks DA receptor subtypes. This strategy has not been fruitful. For example, the partial DA D2 receptor antagonist aripiprazole enhanced cocaine's effects in the laboratory and increased cocaine use in a clinical trial (Tiihonen et al., 2007; Newton et al., 2008). In fact, medications that have the opposite action (i.e. facilitate DA neurotransmission) show efficacy for cocaine dependence (Castells et al., 2010; Pérez-Mañá et al., 2010). Recent research on neurotransmitter systems *other* than DA, particularly NE, has yielded significant advances in defining cocaine's action on brain neurochemistry as it relates to medication development (Weinshenker & Schroeder, 2007). Most important is the finding that promising medications for cocaine dependence, such as sustained-release (SR)-AMPH, SR-methamphetamine (METH) and the dopamine beta hydroxylase (DBH) inhibitor disulfiram more potently alter NE than DA neurotransmission (Rothman et al., 2001).

2.2. Cocaine: effects on NE neurotransmission

Similar to its action on DA, cocaine also blocks 5-HT and NE reuptake to elevate synaptic levels of these neurotransmitters. Studies suggest that 5-HT contributes to some behavioral effects produced by cocaine though NE appears to play a more important role in regulating, more specifically, stimulant-induced increases in DA (Rocha et al., 1998; Filip et al., 2010). Genetically altering NE production in animals or administering drugs that facilitate NE release, or block the synthesis or specific receptor subtypes of NE, significantly alter cocaine's effects (Hameedi et al., 1995; Petrakis et al., 2000; Haile et al., 2003; Carroll et al., 2004; Baker et al., 2007; Weinshenker & Schroeder, 2007; Herin et al., 2010; Schroeder et al., 2010; Oliveto et al., 2011). Nonetheless, the exact role of NE in mediating psychostimulant behavioral and subjective effects in humans remains unclear. One probable mechanism involves NE regulating DA transmission in the mesocorticolimbic circuit. For example, NE cell bodies project to the NAc and VTA from brainstem A1, A2 areas as well

as the locus ceruleus (LC) (Jones & Moore, 1977; Mejías-Aponte, Drouin, & Aston-Jones, 2009; Phillipson, 1979). These projections directly influence DA cell firing whereas noradrenergic neurons projecting to the PFC indirectly affect DA neurotransmission in the NAc by way of excitatory inputs (Swanson & Hartman, 1975; Morrison et al., 1981) (Shi et al., 2000). NE terminals can also take up and release DA with NE in the PFC when LC NE cell bodies are stimulated (Devoto et al., 2001, 2005). Preclinical and clinical studies in humans support the notion that disrupting NE neurotransmission within this circuit blocks cocaine's behavioral effects (Weinshenker & Schroeder, 2007).

2.3. Cocaine: effects on glutamate neurotransmission

GLU neurotransmission also plays a significant role in drug reward and reinforcement and GLU receptors may be therapeutic targets for the treatment of cocaine dependence (Bowers et al., 2010; Schmidt & Pierce, 2010; Kalivas & Volkow, 2011). GLU is the most ubiquitous excitatory neurotransmitter in the brain and is essential for a myriad of processes including neuroplasticity linked to long term potentiation (LTP), long term depression (LTD), extinction, and reward-related learning (Sarti et al., 2007; Chen et al., 2008; Shen et al., 2009; Knackstedt et al., 2010; Novak et al., 2010). Recent preclinical studies reveal that GLU projections from the PFC to the NAc are critical for cue-, stress- and cocaine-primed reinstatement of previously extinguished cocaine self-administration in animals (Cornish & Kalivas, 2000; Bäckström & Hyttiä, 2007) (Bäckström & Hyttiä, 2007) (Ping et al., 2008). The GLU ionotropic receptor agonist AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) infused into the NAc reinstates cocaine self-administration, whereas blocking translation and expression of the AMPA receptor subunit, GLuR1 (by antisense oligonucleotides) attenuates this behavioral effect (Ping et al., 2008).

AMPA receptors have also been implicated in a variety of effects on behavior produced by cocaine (Carlezon & Nestler, 2002; Bowers et al., 2010; Knackstedt et al., 2010). For example, repeated cocaine exposure increases GluR1 levels in the VTA (Fitzgerald et al., 1996). Increasing CREB in the VTA up-regulates GluR1, whereas ablating CREB in a manner that blocks endogenous levels of CREB decreases GluR1 levels (Olson et al., 2005). Pre-synaptic metabotropic mGluR2/3 autoreceptors regulate the release of GLU. Activation of these receptors attenuates cocaine- and cue-induced reinstatement (Anwyl, 1999; Adewale et al., 2006). Consistent with these outcomes antagonism of post-synaptic mGluR5 receptors also blocks cue-induced cocaine-reinstatement (Bäckström & Hyttiä, 2006; Iso et al., 2006). A study using ¹H magnetic resonance spectroscopy in human cocaine abusers revealed that GLU (as a ratio of creatine) is decreased in the anterior cingulate (Yang et al., 2009). Glutamate levels were also positively correlated with years of cocaine use suggesting that the changes in GLU developed as a result of exposure to cocaine (Yang et al., 2009). Taken together, these findings highlight an ever expanding understanding of GLU receptor subtypes in cocaine's behavioral effects and may offer possible pharmacotherapeutic targets for cocaine dependence.

3. Long-lasting drug effects: neuroplasticity

Neuroplastic changes occur in response to exposure to drugs of abuse, the persistence of these changes beyond termination of drug administration suggest these chronic changes may be involved in dependent users increased susceptibility to relapse to drug taking even after a long period of abstinence (e.g., Robinson & Kolb, 2004). Cocaine can induce LTP in the VTA of excitatory afferents onto dopaminergic cells (Ungless et al., 2001), which is mediated by AMPA and N-methyl-D-aspartate (NMDA) glutamatergic receptors (Bellone & Lüscher, 2006; Schumann et al., 2009; Bird et al., 2010; Mameli et al., 2011). Alterations in the VTA induced by chronic cocaine leads to alterations in the NAc, a target of these DA neurons (Conrad et al., 2008; Mameli et al., 2009). These persistent changes seen in both

brain areas at the cellular level are also associated with drug-seeking and drug-taking in rodents that display behavioral characteristics of human addiction and may relate to recurring relapse in cocaine-dependent individuals (Kasanetz et al., 2010). It is apparent that both DA and GLU transmission have important roles in the long-term stabilization of synaptic neurotransmission associated with stimulant administration (Kalivas & O'Brien, 2008).

Taken together, pharmacotherapies that mediate GLU neurotransmission in particular, could theoretically reverse aberrant cocaine-induced neuroplastic changes and prevent future relapse in humans (Szumlinski et al., 2008; Pacchioni et al., 2009) (Szumlinski et al., 2008). Reversing long-lasting neuroplastic changes linked to GLU dysregulation and relapse may provide greater benefit rather than targeting DA neurotransmission directly. As we elaborate elsewhere in this review, GLU from the PFC controls DA neurotransmission in reward circuitry centers such as the NAc. Although much more research is needed, recent studies assessing glutamatergic compounds such as N-acetyl-cysteine (NAC), d-cycloserine and others in humans have shown some promise for cocaine dependence and support on-going assessment (Kalivas & Volkow, 2011).

4. Neurobiological and behavioral consequences of long-term cocaine exposure

Much of our understanding of these abnormalities and consequences of chronic cocaine use have been derived from imaging studies in humans measuring cerebral metabolism, blood flow, blood volume and ligand binding to specific receptor subtypes. Cocaine users show lower rates of glucose utilization as measured with fluorodeoxyglucose and positron emission tomography (PET) (Volkow et al., 1991, 1992; Goldstein et al., 2004). Firm evidence from these studies and others indicate that chronic cocaine use is associated with hypofrontality or a decreased activation of PFC areas, coupled with D2 receptor levels in the ventral striatum (Volkow et al., 1993a). They include (Fig. 1) decreased DA synthesis (Wu et al., 1997), reduced endogenous DA levels (Martinez et al., 2004, 2009b), blunted stimulant-induced DA release (Martinez et al., 2007), reduced D2/D3 receptor levels (Volkow et al., 1993; Martinez et al., 2004, 2009a) but not D1 receptors (Martinez et al., 2009b), increased DAT (Crits-Christoph et al., 2008), up-regulated NET (Fig. 2) (Ding et al., 2010) and dysregulated GLU (Fig. 3) (Yang et al., 2009). Some of these abnormalities are not fully reversed upon prolonged withdrawal, and may therefore represent an example of aberrant cocaine-induced neuroplastic changes associated with cocaine dependence. For example, a long-term study in non-human primates found that D2 receptor availability before exposure to cocaine predicted rates of subsequent cocaine self-administration (Nader et al., 2006). Consistent with the non-human primate study, D2 receptor levels obtained in cocaine-dependent subjects three years previously predicted responses to rewarding stimuli (Asensio et al., 2010). Other brain structural abnormalities have been reported (decreases) in white matter (Moeller et al., 2007; Ma et al., 2009) (Lim et al., 2008; Xu et al., 2010) and gray matter some of which correlate with duration of cocaine use, and are partially reversed upon cessation of drug-taking (Franklin et al., 2002; Makris et al., 2004; Sim et al., 2007; Hanlon et al., 2011). The effects of these changes on behaviors associated with cocaine dependence are less clear. They may in fact represent direct neurotoxic effects of cocaine use — the behavioral implications of which have yet to be elucidated.

Although a number of neurobiological consequences of chronic cocaine exposure have been identified, how these changes result in addictive behavior is not straightforward. Counter to the prevailing assumption that cocaine-dependent individuals experience a greater activation of striatal areas and enhanced subjective responses, cocaine-dependent individuals have decreased striatal activation and blunted subjective responses to stimulants compared to

normal individuals, yet show an increased sensitivity to memory cues associated with drug-taking (Volkow et al., 1993; Wong et al., 2006). Likewise, alcohol-dependent individuals show similar blunted responses (Volkow et al., 1993b; Martinez et al., 2005). These data suggest selective brain receptors and circuits that control drug responsivity are dysregulated in drug-dependent individuals and this may be common across drug classes (Fehr et al., 2008; Lee et al., 2009). Decreased D2 receptor levels are also associated with lower metabolic corticofrontal brain activity that may be associated with many of the deficits seen in cocaine dependence (Volkow et al., 1993; Kalapatapu et al., 2011).

One way to increase treatment efficacy for cocaine dependence would be to reverse cocaine-induced neuroplasticity through targeted pharmacotherapy (Moussawi et al., 2009). Neuroimaging studies show that cocaine-dependent individuals have decreased DA synthesis, low endogenous DA levels, reduced DA release and reduced D2/D3 receptor availability that is associated with orbitofrontal cortex compromise (Wu et al., 1997; Martinez et al., 2004, 2007, 2009a, 2009b). Cocaine-dependent individuals also have increased numbers of striatal DA transporters which may increase DA uptake leading to reductions in post-synaptic DA binding that may further compromise DA neurotransmission (Cris-Christoph et al., 2008) (Table 1). Perhaps decreased DA levels and dopaminergic receptors at baseline (during adolescence for example) may increase likelihood that an individual would find cocaine reinforcing and therefore be at greater risk to develop cocaine dependence. This would imply that increasing dopaminergic neurotransmission, and increasing binding to D2 receptors, would confer protection from cocaine dependence. By extension, medications that increase DA neurotransmission and increase D2 receptor binding would be therapeutic for cocaine dependence (Thanos et al., 2007).

4.1. Cocaine use and cognition

Long-term, repeated use of cocaine is a risk factor for the presence of neurocognitive impairment in humans (Bolla et al., 2003; Jovanovski et al., 2005; Garavan & Hester, 2007), and is especially relevant since increased cognitive impairment is associated with poor retention in treatment programs (Aharonovich et al., 2003, 2006). Also, in a study investigating cocaine-dependent individuals who were HIV+, cocaine-related neurocognitive impairment predicted poor medication compliance (Meade et al., 2011) demonstrating that cocaine dependence can impact progression of otherwise unrelated disease states.

In addition to impacting treatment retention, there is an association between neurocognitive impairment and treatment outcomes (Sofuoglu, 2010). As opposed to chronic cocaine use, acute IV cocaine administration improves performance on the Rapid Visual Information Processing Task (which measures attention) in cocaine-dependent individuals (Johnson et al., 1998), and acute intranasal cocaine administration improves performance on the Digit Symbol Substitution task (which measures speed and information processing) (Higgins et al., 1990). Improvements in neurocognitive functioning after acute stimulant exposure have been found after exposure to other stimulants as well, including AMPH (Johnson et al., 1996) and METH (Mahoney et al., 2010a). These findings suggest that a range of cognitive impairments produced by chronic exposure to cocaine may be reversible, at least partially, by medications that mimic some of the effects produced by cocaine and other stimulants (Brady et al., 2011).

4.2. Cocaine use and impulsivity

Impulsivity has been defined in various ways, most commonly as a lack of inhibitory control, but also rapid responding, lack of persistence, inattentiveness, failure to delay reward gratification, and the selection of smaller immediate rewards over larger delayed

rewards (Rachlin & Green, 1972; Evenden, 1999; Moeller et al., 2001a, 2001b). Continued substance abuse may be an example of impulsive behavior since it involves the failure to take future consequences into consideration and maintain focus on more immediate rewards. For example, chronic substance abusers will repeatedly choose brief but immediate rewards of their substance of choice over larger but delayed positive rewards such as a more stable lifestyle. That impulsivity is a prominent pathological feature of cocaine abuse is supported by the finding that cocaine abusers had higher discount rates for future rewards as compared to controls and alcohol abusers (Kirby & Petry, 2004). Moreover, cocaine-dependent individuals consistently choose smaller immediate monetary rewards rather than larger, delayed rewards when compared to control participants (Coffey et al., 2003). In addition, cocaine-dependent individuals discounted the value of delayed cocaine rewards at a much greater rate than the value of delayed monetary rewards. In other words, a hypothetical reward of \$1000 worth of cocaine lost nearly all of its subjective value after only a 2-month delay, whereas hypothetical monetary rewards lost only half of their subjective value after a 2-month delay. Importantly, one possibility for this disconnect is described by Coffey as being a result of cocaine being viewed as a primary reinforcer, whereas money may be considered a secondary reinforcer (Coffey et al., 2003). Impulsivity may be related to cocaine-induced functional impairments in the orbitofrontal cortex (Bolla et al., 2003; Goldstein et al., 2004, 2010). For example, performance on the Iowa Gambling Task is dependent on the functioning of the orbitofrontal cortex and cocaine-dependent subjects made more disadvantageous choices on this task, and choice consistency factors (reliability of expected choices to be made based on previous, similar choices) differed between cocaine-dependent subjects and controls (Kjome et al., 2010). In addition to contributing to continued drug use, impulsivity is also related to relapses to drug-taking in cocaine abstinent individuals. In a study investigating 1626 cocaine-dependent participants evaluated 6–12 months after treatment, the most commonly cited reason for relapse was “impulsive action with no known cause” (Miller & Gold, 1994). When utilizing the Barrett Impulsivity Scale (BIS), cocaine users with higher scores (indicating high impulsivity) reported more severe withdrawal symptoms (Tziortzis et al., 2011), which may contribute to relapse (Mulaney et al., 1999; Kampman et al., 2002). Taken together, available evidence suggests that impulsivity plays a role in continued cocaine use and could very well be due to dysregulated orbitofrontal cortex abnormalities secondary to chronic cocaine use. Although further research is needed, present evidence suggests that impulsivity in general, should be taken into consideration when developing treatment regimens in order to maximize the probability of a positive clinical outcome.

4.3. Cocaine use and craving

Administration of cocaine to human addicts during abstinence can increase craving for the drug (de Wit & Stewart, 1981; Jaffe et al., 1989). Cocaine-induced craving is important to understand as it may be a critical factor in relapse and may contribute to continued drug dependence. Individuals with high levels of craving show a higher probability of relapse upon discharge after treatment (Rohsenow et al., 2007) and cocaine-dependent individuals when compared to those who met criteria for cocaine-abuse, reported significantly higher levels of craving and were also more likely to make choices for cocaine in the laboratory (Walsh et al., 2010). In that study, cocaine abusers were those who reported cocaine use no more than twice weekly on average for 2 months prior to study admission, and met DSM-IV criteria for cocaine abuse but did not meet diagnostic criteria for cocaine dependence. In contrast, cocaine-dependent participants were required to report cocaine use an average of six or more days per week for 2 months prior to study admission, and meet diagnostic criteria for cocaine dependence, endorsing at least one of the criteria related to “loss of control.”

Despite these data, the relationship between cocaine exposure and craving remains unclear. For example, several reports indicate that cocaine craving increases after cocaine administration in the laboratory (Fischman & Schuster, 1982; Jaffe et al., 1989; Kosten et al., 1992; Ward et al., 1997b; Sofuoglu et al., 2000a, 2000b; Walsh et al., 2000; Nann-Vernotica et al., 2001) whereas others found that cocaine administration had no effect on craving (Romach et al., 1999; Sofuoglu et al., 1999; Foltin & Haney, 2000; Foltin et al., 2003a, 2003b). Due to these discrepancies, a qualitative and meta-analytic review was conducted to investigate this problem in more detail. The results of the qualitative review suggested that the phenomenon of priming (cocaine-induced craving) did not occur consistently across all studies. On the other hand, the quantitative review revealed that cocaine administration was associated with a significant increase in craving for cocaine, and the effect size of this relationship was large (Mahoney et al., 2007). However, the meta-analytic review only included published findings that provided statistics, and since non-statistically significant results are rarely published, the review was skewed to include primarily those that found a significant difference in craving after cocaine administration. In summary, further research is needed to clarify craving in the profile of cocaine abuse, and deciphering its role will aid in determining the value of reducing craving as a meaningful target for cocaine dependence.

4.4. Impulsivity and craving in cocaine users

Craving appears to be closely related to certain aspects of impulsivity (Franken et al., 2006). Studies trying to determine the relationship between impulsivity and craving, however, have produced mixed results. A positive, though not statistically significant correlation between total impulsivity scores (as measured by the BIS) and cocaine craving scores has been reported (Moeller et al., 2001a, 2001b). Conversely, it has been reported that cocaine-dependent individuals have higher levels of craving than those who meet criteria for cocaine-abuse; however, there were no differences between groups on measures of impulsivity (Walsh et al., 2010). To address this discrepancy, our group conducted a study to investigate the relationship between impulsivity and craving. The data show that craving before drug use was significantly correlated with total impulsivity as well as craving after use (Tziortzis et al., 2011). However, the magnitude of the relationship was small indicating that approximately 90–95% of variance was accounted for by unknown factors (Tziortzis et al., 2011). Our data concur with a study in which heavy cocaine users reported significantly greater levels of craving and were more likely to choose cocaine in the laboratory as compared to cocaine users who used cocaine less frequently, yet the groups did not differ in impulsivity (Walsh et al., 2010). While the link between impulsivity and craving for cocaine may appear logical, research does not unequivocally support this association. Additional research further defining the relationship between impulsivity and craving, and the brain substrates that mediate these effects as they relate to cocaine dependence, is needed.

4.5. Cocaine use and psychosis

A number of studies indicate that cocaine use is associated with the development of psychotic-like symptoms. Nearly 70% of cocaine users have been reported to experience highly distressing paranoia following cocaine use (Satek et al., 1991). A separate report indicated that 90% of cocaine users reported delusions of paranoia and 96% reported experiencing hallucinations (Brady et al., 1991). In addition, utilizing the Psychotic Symptom Assessment Scale, Mahoney and colleagues found that a high proportion of cocaine-dependent individuals reported paranoid delusions and auditory hallucinations (59% and 48%, respectively) (Mahoney et al., 2008). Also, gender differences exist, with cocaine-dependent females being more likely to report auditory and tactile hallucinations, whereas males were more likely to report delusions of grandeur (Mahoney et al., 2010b).

4.6. Cocaine use and aggression

It is widely accepted that cocaine use contributes to aggression, criminal violence (Degenhardt et al., 2005; Murray et al., 2008) and impulsivity (Martin et al., 1994; Hollander & Stein, 1995; Brady et al., 1998; Moeller et al., 2002; Bjork et al., 2004; Macdonald et al., 2008). In one report, cocaine-dependent volunteers showed more aggressive behavior in a computerized competitive task (Moeller et al., 1997). This study also revealed that aggression was not necessarily related to cocaine craving, but was associated with the presence of antisocial personality disorder. On the other hand, craving was positively correlated with both impulsivity and aggression (Roozen et al., 2011). Specifically, patients with high impulsivity exhibit both high craving and high aggression levels (Roozen et al., 2011). However, comparable to Moeller et al. (1997), another group found that craving does not have an impact on the association between impulsivity and aggression in this population (Roozen et al., 2011). A retrospective chart review of over three hundred patient visits to a psychiatric emergency facility found that positive urine toxicology for cocaine were not associated with aggressive behavior. In fact, patients positive for cocaine were less frequently aggressive compared to cocaine-negative patients with those demonstrating psychotic symptoms more likely to be admitted (Dhossche, 1999). Finally, a subset of cocaine-dependent individuals characterized by high levels of predisposed trait aggression exhibited more aggressive behavior than other cocaine users (Buss & Perry, 1992; Bushman, 1995; Roozen et al., 2011). Although the link between cocaine use and aggression is commonly assumed to be directly causal the present evidence does not support this assumption. More studies directly focused on this important research topic are needed to parse out the link between cocaine use and aggressive behavior.

4.7. Cocaine use and depression/anxiety

Cocaine users often experience depression (Brienza et al., 2000; Kidorf et al., 2004; Kilbey et al., 1992; Falck et al., 2002; Wild et al., 2005). Specifically, 25–61% of individuals in treatment for cocaine abuse or dependence (Rounsaville et al., 1991) are diagnosed with mood disorders, including specifically major depressive disorder. Moreover, the positive subjective effects produced by cocaine (e.g. the self-reported “high”) has been positively correlated with the severity of depressive symptoms in volunteers who do not meet criteria for major depression (Uslaner et al., 1999; Sofuoglu et al., 2001). The data suggest that individuals experiencing greater depressive symptoms during withdrawal may be more likely to continue to use or relapse during a period of abstinence. Consistent with this, a positive correlation was reported between depressive symptoms and craving (Elman et al., 2002). Similarly, another report showed that depressed cocaine users experienced more severe withdrawal symptoms when compared to non-depressed participants (Helmus et al., 2001). Of additional interest, Sofuoglu and colleagues demonstrated that while cocaine exposure resulted in greater physiologic effects (e.g., heart rate, blood pressure) in participants reporting more severe levels of depression, there were no significant differences in cocaine-induced subjective effects between depressed versus non-depressed subjects (Sofuoglu et al., 2001). However, a recent meta-analysis revealed that the relationship between depressive symptoms and treatment outcomes was not strong (Conner et al., 2008) indicating that depressive symptoms may not play as critical of a role in cocaine use characteristics as originally anticipated. Although mixed, the relationship between cocaine use and depressive symptomology is suggested in a subset of users. Therefore it remains critical to consider comorbid diagnoses (cocaine dependence in combination with a mood disorder) to ensure identification of the most effective treatment.

5. Medication development for cocaine dependence

The remaining portion of this review will focus on medications that have shown positive results for treating cocaine dependence by presumably acting on DA, NE and GLU neurotransmission. Each of these medications is reviewed within the context of their therapeutic action ameliorating known deficiencies in individuals with cocaine dependence.

5.1. Modafinil

Modafinil is a wake-promoting medication indicated for narcolepsy and shift-work somnolence (Jasinski & Kovacevi -Ristanovi , 2000). This medication also has been used to treat attention deficit hyperactivity disorder (ADHD), obstructive sleep apnea, and to augment other medications for the treatment of mild depression (Kumar, 2008). Modafinil's mechanism of action includes increasing histamine, DA and NE levels, promoting GLU neurotransmission, suppressing GABA, and activating the hypocretin–orexin system (Ferraro et al., 1997, 1999; Ishizuka et al., 2003; Madras et al., 2006; Huang et al., 2008; Martínez-Raga et al., 2008; Volkow et al., 2009). Under certain experimental conditions, modafinil may stimulate DA D2 receptors, which may play a role in its wake-promoting effects (Korotkova et al., 2007; Qu et al., 2008; Seeman et al., 2009). Consistent with its actions on DA, NE and GLU, modafinil increases locomotor activity in rodents (Paterson et al., 2010), engenders similar discriminative stimulus effects as that produced by cocaine (Gold & Balster, 1996; Deroche-Gamonet et al., 2002; Paterson et al., 2010) and reinstates extinguished cocaine-induced place conditioning (Bernardi et al., 2009). Unlike classical stimulants such as cocaine or AMPH, modafinil is not self-administered by rodents (Deroche-Gamonet et al., 2002). In fact, modafinil has been shown to have the opposite effect of blocking reinstatement of drug-seeking for METH (Reichel & See, 2010). In non-human primates, modafinil maintains self-administration only at very high doses—which are never used clinically (Gold & Balster, 1996). Similar to other medications that bind to the DAT but have low abuse liability (e.g., bupropion), modafinil appears to increase DA by binding to the DAT in a unique manner (Schmitt & Reith, 2011).

In clinical studies, modafinil has low abuse potential (Jasinski & Kovacevi -Ristanovi , 2000; Rush et al., 2002) and is not self-administered by cocaine-dependent individuals (Vosburg et al., 2010). Indeed, similar to what has been demonstrated on cocaine reinforcement in animals, modafinil attenuates the positive subjective and reinforcing effects produced by cocaine in the laboratory (Dackis et al., 2003; Malcolm et al., 2006; Hart et al., 2008; De La Garza et al., 2011) and reduces cocaine use (Dackis et al., 2005). Modafinil does not appear to decrease cocaine use in cocaine-dependent individuals who are also heavy alcohol users — the reasons for this are unclear (Anderson et al., 2009).

It is presently unknown how modafinil decreases cocaine use and blocks the positive subjective effects of cocaine in cocaine-dependent individuals. It is likely that several aspects of the numerous transmitter systems engaged by modafinil act in concert to exert its therapeutic effects. For example, a recent rodent study demonstrated that modafinil-induced GLU release which activated mGluR2/3 (Fig. 3) receptors accounted for its ability to inhibit reinstatement of morphine-conditioned place preference (Tahsili-Fahadan et al., 2010). The most compelling evidence suggests however that modafinil's effects specific to inhibiting the DAT may be key to its therapeutic actions (Madras et al., 2006; Volkow et al., 2009; Andersen et al., 2010; Newman et al., 2010; Schmitt & Reith, 2011). Thus, the ability of modafinil to rectify the dysregulation imposed on DA and GLU by cocaine may be important for its efficacy for cocaine dependence. Further studies are needed to validate this hypothesis.

Whatever the underlying mechanism, modafinil may be useful as a pharmacotherapeutic agent for cocaine dependence by virtue of its ability to improve cognition. In fact, several reports have shown that modafinil improves cognitive function in healthy volunteers (Turner et al., 2003), adults with ADHD (Turner et al., 2004), and in METH-dependent individuals (Kalechstein et al., 2010; Ghahremani et al., 2011).

5.2. N-acetylcysteine

Medications that reverse changes in GLU transmission imposed by cocaine may be a therapeutic option for cocaine dependence (Kalivas, 2009). The lack of clinically available GLU receptor ligands and the innate complexity of this neurotransmitter system have slowed progress defining GLU's role in psychostimulant dependence.

In the NAc, GLU levels are maintained by the glial cystine-glutamate antiporter, which exchanges 1:1 molecules of cystine to GLU. This antiporter is down-regulated following exposure to cocaine which leads to low levels of basal GLU (Fig. 3) (Baker et al., 2002, 2003) (Baker et al., 2003). Importantly, GLU in the NAc mediates reinstatement of cocaine self-administration in rodents (Baker et al., 2003; Kau et al., 2008). N-acetylcysteine blocks cocaine reinstatement apparently by re-engaging mGluR2/3 autoreceptors that control pre-synaptic GLU release (Baker et al., 2003; Moran et al., 2005). N-acetylcysteine also reverses cocaine-induced neuroplasticity which has been shown to be important in animal models of relapse (Madayag et al., 2007; Moussawi et al., 2009).

Although it is presently unknown whether GLU neurotransmission is definitively compromised in cocaine-dependent individuals, one study has shown using ^1H magnetic resonance spectroscopy that GLU (as a ratio of creatine) was decreased in the anterior cingulate of chronic cocaine users (Yang et al., 2009). Glutamate levels were also positively correlated with years of cocaine use suggesting that GLU changes developed as a result of exposure to cocaine. As noted earlier, N-acetylcysteine reverses cocaine-induced neuroplasticity in rodents and clinical studies generally support N-acetylcysteine's efficacy for cocaine dependence. Specifically, N-acetylcysteine may work by blocking some of cocaine's subjective effects and by attenuating reactivity to drug-cues that elicit craving (LaRowe et al., 2006, 2007; Mardikian et al., 2007; Amen et al., 2011). Larger randomized double-blind placebo controlled trials are needed to confirm these preliminary findings.

5.3. Disulfiram

Disulfiram is a medication indicated for the treatment of alcohol dependence. In several fairly large randomized clinical trials, disulfiram has shown potential as a treatment for cocaine dependence regardless of alcohol use (Carroll et al., 2004). Disulfiram's pharmacokinetic and pharmacodynamic effects are complex (Johansson, 1992; Gaval-Cruz & Weinshenker, 2009). Disulfiram and its metabolite diethyldithiocarbamate chelate copper. Copper sequestration, in turn, compromises many copper-dependent enzymes including D β H, which catalyzes the conversion of DA to NE. Inhibition of this monooxygenase enzyme increases DA and decreases the synthesis of NE (Goldstein et al., 1964; Lippmann & Lloyd, 1969; Major et al., 1979; Hoeldtke & Stetson, 1980). Disulfiram also inhibits carboxylesterase and cholinesterase enzymes that metabolize cocaine, leading to increased plasma levels (Stewart et al., 1979; Benowitz, 1993) and potentiation of its cardiovascular effects (McCance-Katz et al., 1998a, 1998b).

The ability of disulfiram to inhibit D β H and subsequently (Fig. 2) decrease central NE levels is likely responsible for its therapeutic effects in cocaine dependence. Both preclinical and clinical evidence support this notion, though there are some significant complexities (Goldstein & Nakajima, 1967; Rogers et al., 1979; Gaval-Cruz & Weinshenker, 2009) and

other mechanisms may be involved (Yao et al., 2010). For example, NE levels are reduced in both knock-out mice devoid of D β H and in normal mice following chronic disulfiram treatment. Disulfiram treatment renders animals hypersensitive to the locomotor activating effects of cocaine and similar hypersensitivity is observed in untreated D β H knock-out mice (Haile et al., 2003; Schank et al., 2006). In contrast, acute treatment with disulfiram has the opposite effect and decreases locomotor behavior (Maj et al., 1968).

Disulfiram's effects were more clearly demonstrated in a recent study in rats that found that doses of disulfiram that decrease central NE production secondary to D β H inhibition attenuated drug-induced reinstatement of cocaine seeking behavior, whereas lower doses of disulfiram did not (Schroeder et al., 2010). Studies using the more selective and potent D β H inhibitor, nopicastat, lend support for this enzyme as the therapeutic target of disulfiram (Stanley et al., 1997). Preliminary studies in humans have shown that nopicastat alters the positive subjective effects of cocaine similarly to that of disulfiram (Cunningham et al., 2010a, 2010b). These data provide further support for D β H inhibition, and subsequent decrease in NE neurotransmission, as the primary mechanism by which disulfiram decreases cocaine use (Schroeder et al., 2010).

Clinical studies assessing disulfiram's impact on cocaine's effects have also produced seemingly contradictory results. Regarding the subjective effects of cocaine, disulfiram treatment has been reported to decrease the positive subjective effects of cocaine (Baker et al., 2007), increase its negative effects (Hameedi et al., 1995), or produce no changes (McCance-Katz et al., 1998a,b). Results from randomized clinical trials assessing therapeutic efficacy of disulfiram for cocaine dependence also appear complex. For instance, studies have found that disulfiram treatment decreases (Carroll et al., 1993; Higgins et al., 1993; Carroll et al., 2000; George et al., 2000; Grassi et al., 2007) or produces no change (Pettinati et al., 2008) in cocaine use. Patients in the study by Pettinati et al. were also dependent on alcohol, and only 1/3 took >80% of their disulfiram doses, which likely contributed to the lack of efficacy for disulfiram in this study. Interestingly, results from a recent large clinical trial suggest that low doses of disulfiram increase cocaine use (Oliveto et al., 2011). We have also observed striking differences in the effects of disulfiram of cocaine-mediated effects based on dose; low doses increase, and high doses decrease, the reinforcing effects of cocaine in humans (Haile et al., 2012). Parallel results were obtained for the cardiovascular effects produced by cocaine. These data would explain why higher doses of disulfiram reduced cocaine use in clinical trials whereas lower doses of disulfiram increased cocaine use. The mechanism of this dose-response is unclear, but may involve differential effects of disulfiram on NE projections impacting α 1 and α 2 receptors or even augmenting cocaine's ability to increase DA levels (Devoto et al., 2011). Regardless of the mechanism, these findings have compelled some investigators to discount disulfiram as a potential treatment for cocaine dependence (Pani et al., 2010).

Reductions in NE during disulfiram treatment may have other benefits for cocaine users. Early studies showed that cocaine-dependent individuals have dysregulated noradrenergic system functioning and are vulnerable to panic anxiety during acute discontinuation of cocaine use (McDougle et al., 1994). Of interest, propranolol, a mixed β 1/ β 2 noradrenergic antagonist, significantly reduces withdrawal symptoms in cocaine-dependent patients (Kampman et al., 2001). A recent study also indicated propranolol may reverse some aspects of cognitive impairment associated with cocaine withdrawal (Kelley et al., 2007). Treatment with carvedilol a mixed α 1/ β 1/ β 2 antagonist reduced smoked cocaine self-administration in non-treatment seeking cocaine-dependent individuals (Sofuoglu et al., 2000a). These studies further reinforce NE's role in cocaine dependence and provide evidence of additional therapeutic actions of disulfiram.

Disulfiram inhibits aldehyde dehydrogenase and upon ingestion of alcohol results in elevated acetaldehyde. Increased acetaldehyde produces the so-called 'disulfiram-alcohol reaction' that is aversive, and considered the main mechanism by which disulfiram is efficacious as a treatment for alcohol dependence. Because a large percentage of cocaine-dependent individuals either abuse or are dependent upon alcohol (Grant & Harford, 1990; Closser & Kosten, 1992) concern has been raised regarding the disulfiram-alcohol reaction occurring in combination with cocaine resulting in possible adverse cardiac events (Roache et al., 2011). Although a search of the medical literature did not yield any reports of death due to the combination of disulfiram, alcohol and cocaine, there are documented fatalities of disulfiram and alcohol alone (Becker & Sugarman, 1952; Oesterreich, 1966; Amadoe & Gazdar, 1967) and in combination with other medications that inhibit aldehyde dehydrogenase (Cina et al., 1996). While the treating physician should always be mindful of potential adverse events in those individuals who combine alcohol and cocaine while being treated with disulfiram, it is fairly clear that medications that more selectively target D β H and do not block peripheral metabolism of cocaine, or interact with alcohol, will prove to be safer (as well as more effective) for treating cocaine dependence.

5.4. Prazosin/doxazosin

Prazosin and the longer acting compound doxazosin are α 1-adrenergic receptor antagonists. Both medications have therapeutic indications for hypertension and benign prostatic hypertrophy (Miller, 2008). Consistent with its mechanism of action, prazosin has shown efficacy in treating symptoms of post-traumatic stress disorder (PTSD) (Cukor et al., 2009) likely because these individuals have a hypersensitive noradrenergic system characterized by increased NE release and receptor sensitivity (Taylor et al., 2008a, 2008b). This hypersensitivity is associated with disruption in sleep and vivid nightmares. Several clinical trials have shown that prazosin significantly improves these symptoms (Raskind et al., 2007; Taylor et al., 2008a, 2008b). Prazosin's ability to improve PTSD symptoms suggests that it may also have efficacy for attenuating the impact of environmental stressors that can trigger relapse to drug-seeking and -taking (Kosten et al., 1988).

As discussed, pre-clinical studies in animals clearly implicate nor-adrenergic mechanisms in mediating some of the behavioral effects produced by stimulants. Evidence continues to accumulate that α 1-adrenergic receptors are particularly crucial. NE activation of cortical α 1-adrenergic receptors increases NAc DA and enhances stimulant-induced locomotor activity, and these effects are blocked by infusion of prazosin directly into the PFC (Blanc et al., 1994; Darracq et al., 1998; Drouin et al., 2002). In addition, peripheral administration of prazosin attenuates cocaine-induced locomotor activity (Snoddy & Tessel, 1985).

Adrenergic α 1_b receptor knockout mice also show decreased stimulant-induced activity (Drouin et al., 2002). Similar to disulfiram, systemically administered prazosin does not reduce maintenance of cocaine self-administration (Woolverton, 1987), but rather blocks drug-induced reinstatement of cocaine-seeking behavior (Zhang & Kosten, 2005; Schroeder et al., 2010). Taken together however, present evidence supports the α 1 receptor as a possible therapeutic target for cocaine dependence.

Prazosin has a short elimination half-life of 2–3 h in humans and this limits its clinical utility as a treatment for cocaine dependence. The α 1 receptor antagonist doxazosin, by contrast, has a half-life of 22 h, making doxazosin a better medication candidate. Newton and colleagues recently showed using a double-blind placebo-controlled within-subjects experimental design that doxazosin (4 mg/day for 9 days) decreased cocaine's (20 and 40 mg) positive subjective effects in non-treatment seeking cocaine-dependent individuals (Newton et al., 2012). Although preliminary, this study suggests that α 1 receptor antagonism can decrease the positive subjective effects of cocaine and that doxazosin may be a viable treatment for cocaine dependence. These data also support findings from pre-

clinical studies showing that prazosin decreases the behavioral effects of cocaine. Laboratory studies testing whether doxazosin decreases cocaine self-administration in cocaine-dependent individuals, as well as large out-patient clinical trials are needed to extend and confirm these promising preliminary findings.

5.5. Sustained-release AMPH/METH

Medication development for cocaine dependence has primarily focused on antagonist-like pharmacological agents that block the reinforcing effects of cocaine. One premise behind antagonist development is that extinction of drug-taking behavior could be achieved by blocking the pleasurable subjective effects produced by cocaine. This seems counterintuitive based on pre-clinical studies on the maintenance of cocaine self-administration wherein pretreatment with antagonists, particularly DA antagonists, increase cocaine self-administration in rodents (De Wit & Wise, 1977; Haile & Kosten, 2001), as well as clinical studies in which treatment with DA antagonists do not reduce cocaine use in humans (Oluoha et al., 1997). In contrast, DA agonists and indirect agonists decrease cocaine self-administration in rodents and monkeys (Negus & Mello, 2003; Negus et al., 2009). Consistent with these results, studies in stimulant-dependent humans using sustained release AMPH (SR-AMPH) have shown notable promise (Herin et al., 2010). Although this has been termed the “agonist substitution approach” by analogy to the use of methadone or buprenorphine for the treatment of opioid dependence, evidence indicates that the therapeutic effects of these medications is likely more related to correcting deficiencies in central DA neurotransmission (see Table 1).

One concern regarding using stimulants to treat cocaine dependence is abuse liability. The speed at which stimulants cross the blood brain barrier and activate dopaminergic circuitry contributes to their reinforcing effects and abuse liability (Volkow et al., 2000). Stimulant drugs formulated in slow-release preparations have lower abuse liability compared to immediate-release preparations (IR) (Jasinski & Krishnan, 2009). Accordingly, laboratory studies and out-patient clinical trials show that SR-AMPH and SR-METH reduce the subjective effects and cocaine use in dependent individuals (Grabowski et al., 2001, 2004; Mooney et al., 2009; Rush et al., 2009, 2010). In general, present evidence supports the use of low abuse liability SR-, but not IR-, formulations of stimulant medications for cocaine dependence.

The mechanisms that underlie the beneficial effects of stimulant medications for cocaine dependence are unknown but could be related in part to the ability of these compounds to correct deficiencies in monoaminergic neurotransmission mentioned earlier (see Table 1). Consistent with this, at doses used to treat diseases such as ADHD, refractive obesity, and narcolepsy, SR-AMPH and SR-METH both increase DA synthesis and neurotransmitter release, increase activity in cortical brain areas, improve working memory and impulse control; all of which are compromised in cocaine-dependent individuals (Martinez et al., 2004, 2007, 2009a, 2009b; Narendran et al., 2009). Further, SR-AMPH and SR-METH alter the DAT and induce DA efflux possibly correcting central hypodopaminergic tone (Table 1) characteristic among cocaine-dependent individuals (Sulzer et al., 2005; Martinez et al., 2007). Indeed, DA neurotransmission or tone as measured by methylphenidate-induced displacement of raclopride predicts relapse to drug taking after a period of abstinence in stimulant abusers (Wang et al., 2011) and response to treatment (Martinez et al., 2011). Other evidence suggests that the basis for the efficacy of SR-AMPH and SR-METH for reducing cocaine use may have more to do with their action on noradrenergic neurotransmission. NE modulates reinstatement of cocaine-seeking in animal models of relapse (Weinshenker & Schroeder, 2007) and SR-AMPH and SR-METH are more potent releasers of NE than DA (Rothman et al., 2001). NE cell bodies located in the LC project diffusely throughout the brain innervating the VTA, NAc, and other areas implicated in

cocaine's effects (Smythies, 2005). Activation of LC neurons increases VTA DA neuronal firing (Lategan et al., 1990) as does NE in the PFC (Blanc et al., 1994). Whereas acute AMPH inhibits DA neurons in the VTA that are linked to the reinforcing effects produced by cocaine, chronic treatment is associated with the opposite effect of excitation (Kamata & Rebec, 1984). On the other hand, chronic treatment with stimulants produces tolerance to subsequent pharmacological challenges with cocaine suggesting another possible mechanism by which SR-AMPH and SR-METH may work in the treatment of cocaine-dependence (Peltier et al., 1996; Negus & Mello, 2003; Chiodo et al., 2008). In fact, in contrast to acute administration that results in inhibition of neural firing, chronic treatment with AMPH results in neuronal excitation in the VTA and this may account for 'tolerance' to the reinforcing effects of cocaine. Indeed, chronic d-AMPH treatment decreases the reinforcing effects of cocaine in rats (Peltier et al., 1996) and monkeys (Negus & Mello, 2003). Negus and Mello (2003) provided the most convincing preclinical data demonstrating AMPH-induced tolerance to cocaine. Their experiments showed that over twenty-eight consecutive days of d-AMPH treatment cocaine self-administration was reduced to near zero levels (Negus & Mello, 2003). Importantly, cocaine self-administration slowly resumed to normal levels following discontinuation of d-AMPH providing evidence of tolerance.

In summary, formulations of AMPH and METH that provide sustained and regulated peripheral drug levels and reduced abuse liability have shown some promise in reducing cocaine use in cocaine-dependent individuals. Some argue that these medications represent a 'replacement therapy' similar to the methadone model for opioid dependence (Herin et al., 2010). Preclinical data presented earlier indicates that chronic AMPH/METH decreases cocaine's reinforcing effects by producing tolerance, not substituting, for cocaine per se. In addition, AMPH/METH increases DA neurotransmission which is low in cocaine-dependent individuals. It is possible that correcting decreased DA tone may also contribute to AMPH/METH's therapeutic potential for cocaine dependence. Consistent with this idea, low DA neurotransmission is associated with relapse, whereas treatment strategies that increase DA result in decreased cocaine use (Martinez et al., 2011).

5.6. Methylphenidate

Methylphenidate is a stimulant medication indicated for ADHD that increases synaptic levels of NE and increases DA in the NAc (Volkow et al., 2002; Weikop et al., 2007). Some concerns have been raised about the risks associated with using stimulant medications like methylphenidate to treat cocaine dependence, yet there is evidence that they can be used safely and appear efficacious. For example, although a small study showed no reduction in cocaine use with IR-methylphenidate (Schubiner et al., 2002), an open label study in cocaine-dependent adults with ADHD showed that those treated with IR-methylphenidate (20 mg three times a day) had decreased cocaine use and improved ADHD symptoms (Somoza et al., 2004). Similarly, Levin et al. (2007) showed in a double-blind placebo controlled clinical trial in cocaine-dependent individuals with ADHD that SR-methylphenidate improved ADHD symptoms compared to placebo and reduced cocaine use (Levin et al., 2007). Maintenance therapy with SR-methylphenidate (40 and 60 mg) in cocaine-dependent individuals with ADHD reduced the subjective "high" and "good drug effect" of cocaine (16 and 48 mg/kg, IV) and decreased choice for cocaine over a monetary alternative (Collins et al., 2006). A drug interaction study in non-treatment seeking cocaine-dependent individuals without ADHD showed that methylphenidate (60 and 90 mg) decreased positive subjective effects produced by IV cocaine (20 and 40 mg, IV) (Winhusen et al., 2006). However, one clinical trial in cocaine-dependent individuals without ADHD found no benefit of methylphenidate (IR-methylphenidate 5 mg then SR-methylphenidate 40 mg/day) for reducing cocaine use (Grabowski et al., 1997). Nonetheless, the available evidence generally supports that SR-methylphenidate is safe and effective in reducing

ADHD symptoms in cocaine-dependent individuals with ADHD. These studies also suggest that the SR-methylphenidate formulation may be a better choice than IR-methylphenidate for reducing cocaine use. Indeed, IR-methylphenidate is reinforcing whereas the SR formulation is less so. New osmotic-release methylphenidate (OROS) is associated with negligible positive subjective effects and low abuse liability (Spencer et al., 2006). Clinical trials have yet to be completed testing whether OROS methylphenidate may be beneficial for cocaine-dependent individuals with or without ADHD. Taken together, these data show that formulation and methylphenidate dose are crucial for efficacy to reduce cocaine use.

The therapeutic action for methylphenidate is unclear but may involve increasing D2/D3 receptor levels and DA neurotransmission in the orbitofrontal cortex. In rodents, oral methylphenidate treatment increased D2/D3 receptor levels following 8 months, but not 2 months of treatment (Thanos et al., 2007). Moreover, rats treated with methylphenidate for 8 months also showed decreases in cocaine self-administration. Whether chronic methylphenidate increases D2/D3 receptor levels in cocaine-dependent individuals remains to be tested. Methylphenidate may also be beneficial by increasing DA neurotransmission in the orbitofrontal cortex that may contribute toward reversing the metabolic hypofrontality, which has been commonly reported in cocaine-dependent subjects (Volkow et al., 1992). Other studies confirm this, showing that methylphenidate treatment positively influences PFC/orbitofrontal structures involved in affective drive and executive functioning (Goldstein et al., 2002). In general, methylphenidate-enhancement of orbitofrontal cortex functioning may also play a role in attenuating compulsive drug-seeking behaviors by decreasing reactivity to cocaine-associated cues that elicit craving and relapse (Volkow et al., 2010) and enhance emotional control and cognitive tasks regulated by these cortical structures (Goldstein et al., 2010). Ongoing research continues to provide further insight into the therapeutic effects of methylphenidate for cocaine dependence.

6. Summary and conclusions

Pre-clinical and clinical studies continue to define the complex pharmacology and pharmacodynamics of cocaine from the molecular to the behavioral level. Research has determined neuroplastic changes in those with cocaine dependence and this is in line with the ability of the stimulant to induce synaptic plasticity in brain circuits linked to reward learning. Human imaging studies have identified changes in limbic brain areas related to DA neurotransmission that may signal a vulnerable phenotype for cocaine dependence and also provide guidance in identifying suitable therapeutic targets. These insights further support the characterization of cocaine dependence as a brain disease with biologically identifiable pathologies and underscore the urgent need to develop efficacious treatments. Leading approaches include developing pharmacotherapies that increase basal DA levels, increase dopaminergic tone and D2/D3 receptor levels, enhance PFC/orbitofrontal functioning, reverse aberrant cocaine-induced neuroplasticity, and block increases in NE and GLU neurotransmission linked to relapse. Although DA still remains central to the positive reinforcing effects produced by cocaine, there is sound scientific evidence that evaluating potential medications that act on NE and GLU neurotransmitter systems have, and will, continue to show promise as targets for possible treatments for cocaine dependence.

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Fig. 1.

Hypothetical dopamine (DA) synapse demonstrating deficiencies observed in cocaine-dependent individuals (see Table 1) and primary targets of potential pharmacotherapies to reverse these deficiencies. (1) SR-AMPH/SR-METH, modafinil and methylphenidate increase DA neurotransmission and DA levels that are low (2) in cocaine-dependent individuals. (3) Chronic methylphenidate may increase low levels of D2/D3 receptors and likely antagonize cocaine's effects by occupying the DAT (4). (5) Prazosin and doxazosin target noradrenergic $\alpha 1$ receptors that control cocaine-induced DA neurotransmission and block cocaine-induced reinstatement of cocaine self-administration in animals. Preliminary studies in humans show that doxazosin also attenuates cocaine's subjective effects. Disulfiram also alters central DA but its primary therapeutic effects are due to profound decreases in NE that would activate $\alpha 1$ receptors (5).

Fig. 2.

Hypothetical noradrenergic (NE) synapse demonstrating dysregulated neurotransmission observed in cocaine-dependent individuals and primary targets of potential pharmacotherapies to ameliorate these abnormalities. (1) Disulfiram inhibits the enzyme D β H responsible for the conversion of DA to NE profoundly decreasing central NE that is presumably increased (2) in cocaine-dependent individuals since NET numbers (3) are also increased in parts of the brain involved in stress. SR-AMPH/SR-METH more potently increase NE (2) than DA and likely through chronic treatment produce tolerance to cocaine's reinforcing effects. (4) Prazosin and doxazosin are NE $\alpha 1$ antagonists and block drug-induced reinstatement of cocaine-seeking. Disulfiram treatment, which depletes central NE, has similar effects to prazosin and doxazosin on reinstatement. Modafinil and methylphenidate also alter NE levels that may play a role in their therapeutic effects.

Fig. 3.

Hypothetical glutamatergic (GLU) synapse with juxtapsed glial cell demonstrating abnormalities observed in cocaine-dependent individuals and primary targets of potential pharmacotherapies to address these deficits. (1) Normal GLU neurotransmission is compromised in cocaine-dependent individuals. Chronic cocaine down-regulates glial glutamate transporter-1 (GLT-1) and the cystine-glutamate exchanger (2) and disrupts mGluR2/3 and mGluR5 (3)(4) influence on GLU tone and neuroplasticity. N-acetylcysteine restores functional GLT-1 and the exchanger in turn, normalizing GLU tone by acting on mGluR2/3 and mGluR5. Modafinil also increases GLU neurotransmission and blocks reinstatement of cocaine seeking and reinstatement of drug-induced conditioning. Modafinil's ability to block drug-induced conditioning is mediated by mGluR2/3 receptors. (5) Noradrenergic $\alpha 1$ receptors on GLU terminals in the NAc alter cocaine's behavioral effects. Prazosin and doxazosin antagonists may exert their therapeutic effect partly by decreasing GLU in response to cocaine. Disulfiram treatment, which depletes central NE, may also reduce GLU influence on DA cells required for cocaine's effects.

Table 1

Central abnormalities identified using neuroimaging in cocaine-dependent individuals.

Compromised structure/function	Brain region	Imaging technique	Change	Reference
Baseline endogenous DA levels	Striatum	PET	↓	Martinez et al., 2009a, 2009b
Stimulant-induced DA release	Striatum	PET	↓	Volkow et al., 1997,
		SPECT	↓	
		PET	↓	Martinez et al., 2007
DAT	Striatum			Malison et al., 1998
		PET	NC	Volkow et al., 1996
Dopamine D1 receptors	Striatum	SPECT	NC	Martinez et al., 2009b
Dopamine D2/D3 receptors	Striatum	PET	↓	Volkow et al., 1990, 1993a
		SPECT	↓	Martinez et al., 2004, 2007, 2009a
NET	Thalamus	SPECT	↑	Ding et al., 2010
	Dorsomedial thalamic nucleus		↑	
	Locus coeruleus		↑	
Glutamate	Anterior cingulate	¹ H MRS	↑	Yang et al., 2009
Brain glucose/metabolism	Anterior cingulate/orbitofrontal cortex	FDG PET	↓	Volkow et al., 1993a
		FDG PET	↓	Volkow et al., 1999

DA — dopamine, PET — positron emission tomography, SPECT — single photon emission tomography, DAT — dopamine transporter, NC — no change, NET — norepinephrine transporter, FDG — fluorodeoxyglucose, MRS — magnetic resonance spectroscopy.