Cocaine Addiction: Changes in Excitatory and Inhibitory Neurotransmission

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1. Introduction

The principal routes of cocaine administration are oral, intranasal, intravenous, and inhalation. The slang terms for these routes are, respectively, "chewing," "snorting," "mainlining," "injecting," and "smoking" (including freebase and crack cocaine). Cocaine use ranges from occasional use to repeated or compulsive use, with a variety of patterns between these extremes. There is no safe way to use cocaine. Any route of administration can lead to absorption of toxic amounts of cocaine, allowing to acute cardiovascular or cerebrovascular emergencies that could result in sudden death. Repeated cocaine use by any route of administration can produce addiction and other adverse health consequences. Those who snort or sniff cocaine through their noses suffer damage to their nasal and sinus passages. These include nasal crusting, nosebleeds, nasal congestion, irritation, facial pain caused by sinusitis and hoarseness.

Cocaine addiction changes the responsiveness of the brain to various neurotransmitters or chemicals. The development of drug addiction involves persistent cellular and molecular changes in the Central Nervous System. The brain dopamine, GABA and glutamate systems play key roles in mediating drug-induced neuroadaptation. We show some physiological changes that can occur in some key pathways in which glutamate, dopamine and GABA receptors are involved. These chemical changes cause different effects in users, including: anxiety, confusion, dizziness, psychosis, headaches and nausea.

Cocaine use and addiction affects the sympathetic nervous system (which controls automatic functions such as breathing, heartbeat, etc.). This system secretes adrenaline which raises ones heart rate, narrows blood vessels and significantly increases blood pressure. Chest pain, heart attacks and strokes are common side effects of cocaine use.

The most widely studied neurobiological characteristic of cocaine addiction is the role played by dopamine transmission. It is clear that enhanced dopamine transmission in neurons projecting from the ventral mesencephalon to the limbic forebrain, including the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc), is the pharmacological target for cocaine-induced reinforcement and locomotor stimulation (O' Brien., 2001) However, persistence of the behavioral characteristics of cocaine addiction, such as paranoia (sensitization) and the propensity to relapse years after the acute rewarding effects of the drug have disappeared, indicates that there must also be neuronal substrates undergoing

long-term neuroplastic changes. Although studies have endeavored to identify enduring changes in dopamine transmission that might underlie behavioral sensitization and the reinstatement of drug-seeking (relapse), the results have not been entirely consistent with an obligatory role for dopamine.

Addiction can be viewed as a form of drug-induced neural plasticity. One of the best-established molecular mechanisms of addiction is up-regulation of the cAMP second messenger pathway, which occurs in many neuronal cell types in response to chronic administration of opiates or other drugs of abuse. This up-regulation and the resulting activation of the transcription factor CREB appear to mediate aspects of tolerance and dependence. In contrast, induction of another transcription factor, termed 1FosB, exerts the opposite effect and may contribute to sensitized responses to drug exposure. Knowledge of these mechanisms could lead to more effective treatments for addictive disorders.

2. The neurobiology of cocaine addiction

Dopamine acts as a modulator for many nerve cells throughout the brain. Dopamine is responsible for keeping those cells operating at the appropriate levels of activity to accomplish our needs and aims (Nestler., 2005). Whenever we need to mobilize our muscles or mind to work harder or faster, dopamine drives some of the involved brain cells to step up to the challenge (Nestler., 2005). The targets in brain and other organs are shown in figure 1.
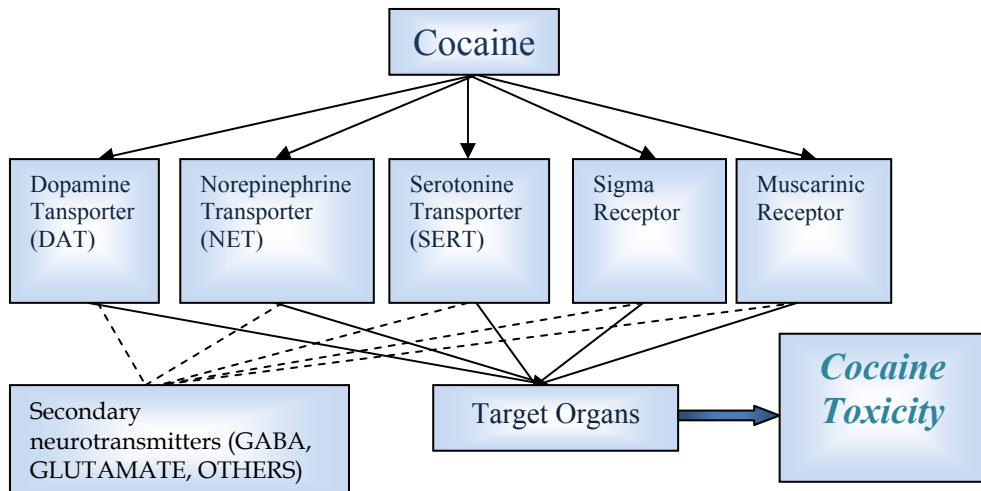

Fig. 1. Cocaine and receptors associated with its toxicity. Continuous lines show the main target organs affected; dashed lines represent the secondary neurotransmitters associated. (Adapted from Nestler., 2005)

Dopamine is originated in dopaminergic neurons and launch them into their surroundings. Some of the free-floating dopamine molecules latch onto receptor proteins on neighboring cells. Once attached, dopamine stimulates the receptors to alter electrical impulses in the receiving cells and thereby alter the cells' function. To keep the receiving cells in each brain region functioning at appropriate intensities for current demands the dopaminergic cells continually increase and decrease the number of dopamine molecules they launch. They

further regulate the amount of dopamine available to stimulate the receptors by pulling some previously released dopamine molecules back into themselves (Nestler., 2005).

One of the most addictive drugs is cocaine. Cocaine can act mainly on the mesoaccumbens dopamine (DA) pathway of the midbrain, extending from the ventral tegumental area (VTA) to the nucleus accumbens (NAc). This pathway is also known as the reward pathway as it is the area of the brain that is activated when someone has a pleasurable experience such as eating, sex, or receiving praise. Cocaine interferes with the dopamine control mechanism: It ties up the dopamine transporter. As a result, with cocaine on board, dopamine molecules that otherwise would be picked up remain in action. Dopamine builds up and overactivates the receiving cells. However, DA is not the only system affected by cocaine. Glutamate and neurotransmission mediated for this aminoacid is also modified and has an importantt role in the mechanism of this drug addiction.
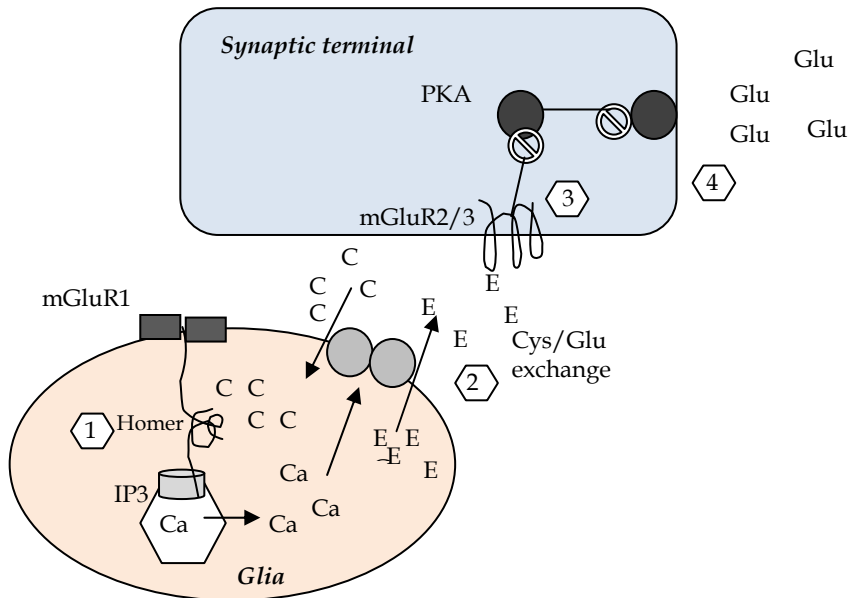

Fig. 2. The potential mechanisms regulating glutamatergic transmission in the NAc that are involved in the reinstatement of drug-seeking behavior. The cocaine-induced changes in extrasynaptic glutamate release outlined below are postulated to increase the signal-to-noise ratio of synaptically released glutamate, thereby facilitating drug-seeking. 1. Homer protein is reduced in the nucleus accumbens, causing a reduction in signaling via mGluR1 receptors through inositol trisphosphate (IP3) receptor regulation of internal calcium (Ca) stores. 2. Because glutamate release stimulated by mGluR1 receptors results from activation of the cystine/glutamate exchanger, it is proposed that down regulated mGluR1 signaling may mediate the reduced activity of the cystine/glutamate exchanger produced by chronic cocaine administration. 3. The reduced heteroexchange of extracellular cystine (C) for intracellular glutamate (E) in glia results in reduced basal extracellular glutamate and reduced tone on mGluR2/3 presynaptic autoreceptors. 4. This reduced tone, accompanied by mGluR2/3 residing in a more phosphorylated (desensitized) state, results in reduced inhibitory regulation of synaptically released glutamate (Glu) (Adapted from Kalivas., 2004)

The way in which this sequence of adaptations could synergize to dysregulate presynaptic glutamate transmission in cocaine addiction is illustrated in Figure 2. This hypothetical model describes how reduced Homer1bc could account for reduced activity of the cystine-glutamate exchanger and the accompanying reduced basal levels of extracellular glutamate. The reduced levels of glutamate, combined with desensitization of the mGluR2/3 receptor, results in a loss of regulatory feedback on synaptic glutamate release. Thus, lower basal levels of glutamate, combined with increased release of synaptic glutamate in response to activation of prefrontal cortical afferents to the NAc, results in an amplified signal and behavioral drive to engage drug seeking (e.g. to relapse). In addition to adaptations in presynaptic and possibly glial release of glutamate that regulate the expression of sensitization and/or reinstatement   a variety of changes in postsynaptic glutamate transmission have been documented in the NAc. Interestingly, although presynaptic release of glutamate was augmented by withdrawal from repeated cocaine, most data indicate a reduction in postsynaptic responses to glutamate (Kalivas., 2004).

3. Brain changes during cocaine addiction

Animal studies of cocaine´s action have focused on a set of subcortical gray matter of some structures as paralimbic cortices, that are involved in the mediation of reward and reinforcement, most notably the ventral tegmental area of the midbrain, the nucleus accumbens, the amygdala, and regions of the prefrontal cortex (Makris et al., 2004). Existing studies of brain structure in cocaine users have reported abnormalities only in brain regions connected to the amygdala, such as the orbitofrontal and anterior cingulate cortex (Franklin et al., 2002; Matochik et al., 2003). Markis et al., (2004) sought to evaluate the hypothesis that topological and volumetric abnormalities may exist in the amygdala of cocaine-dependent subjects that may represent a predisposition to cocaine addiction, or an adaptation to protracted exposure to the drug. Amygdala volume and topology were assessed by segmentation-based morphometric analysis, and absolute quantitative volumetric measures were performed. It was observed that amygdala volume of cocaine-dependent subjects was significantly smaller than the one of matched controls.

The amygdala volumes of cocaine-dependent subjects were similar for each hemisphere, whereas those of their matched controls had clear laterality differences. In addition, amygdala volume in addicts did not correlate with (1) measures of anxiety or depression, (2) any measure of the amount of cocaine use, or (3) age at which cocaine use began (Makris et al., 2004)

Barrós-Loscertales et al., (2011) reported reduced gray matter (GM) volume in the striatum and in the supramarginal gyrus. Likewise, another set of cortical and subcortical structures, such as the amygdala, the insula and dorsolateral prefrontal cortex, were seen to have volume reductions related to years of cocaine exposure (Barrós-Loscertales et al., 2011). All these structural changes associated with cocaine addiction seem to merge in the striato-cortico-limbic circuitry linked not only to addiction, but also to the wider set of disinhibitory disorders (Barrós-Loscertales et al., 2011). Although causal relationships are very difficult to determine in human studies, the significant relationship between years of use and reduced GM volumes are consistent with these volumetric effects arising from the cumulative exposure to cocaine or the concomitant lifestyle (e.g., stress) that accompanies prolonged drug use (Yücel et al., 2008).

In other aspects, Ersche et al., (2011) found some differences between healthy and cocaine users, specially in the gray matter abundance in some regions of the brain. There was widespread significant loss of grey matter in orbitofrontal cortex bilaterally in the cocaine user group. Grey matter volume was also abnormally reduced in the insula, the medial frontal and anterior cingulate cortex, temporoparietal cortex and the cerebellum. In contrast to this extensive system of decreased cortical grey matter volume, cocaine users also showed a significant increase of grey matter volume mainly localized to basal ganglia structures (including putamen, caudate nucleus and pallidum), and cerebellum (figure 3).
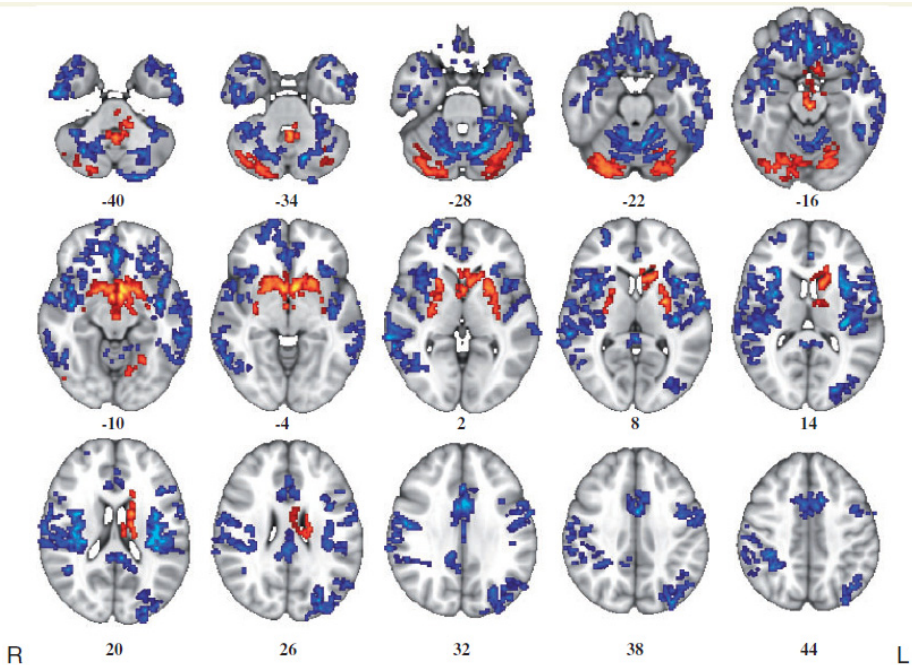

Fig. 3. Whole-brain maps of significant differences in grey matter volume between healthy volunteers and cocaine users. Voxels coloured blue indicate brain areas in which cocaine users have reduced grey matter volume compared with healthy volunteers, and voxels coloured red indicate brain areas in which cocaine users have abnormally increased grey matter volume. These results were generated by permutation testing of voxel cluster statistics with cluster-wise P50.001, at which level we expect less than one false positive cluster per map. The statistical results are overlaid on the FSL MNI152 standard T1 image and the numbers beneath each section of the image refer to its position (mm) relative to the intercommissural plane in standard stereotactic space. L = left; R = right. (Ersche et al., 2011)

In addition, it has been found that the caudate enlargement in cocaine users was associated with significant attentional impairments, whereas the reduction in grey matter in the orbitofrontal cortex was associated with cocaine-related compulsivity. The abnormal changes in grey matter in the striatum and in the orbitofrontal cortex were both related to the duration of cocaine abuse (Ersche et al., 2011).

In another interesting description, Ersche et al., (2011) showed some maps of brain regions demonstrating significant association between grey matter volume and measures of duration of cocaine use, compulsivity and impulsivity in the group of cocaine users (figure 4). This study allow see that is possible find some positive and negative correlations between grey matter and duration of cocaine use, or compulsive cocaine taking or impulsivity in cocaine users.
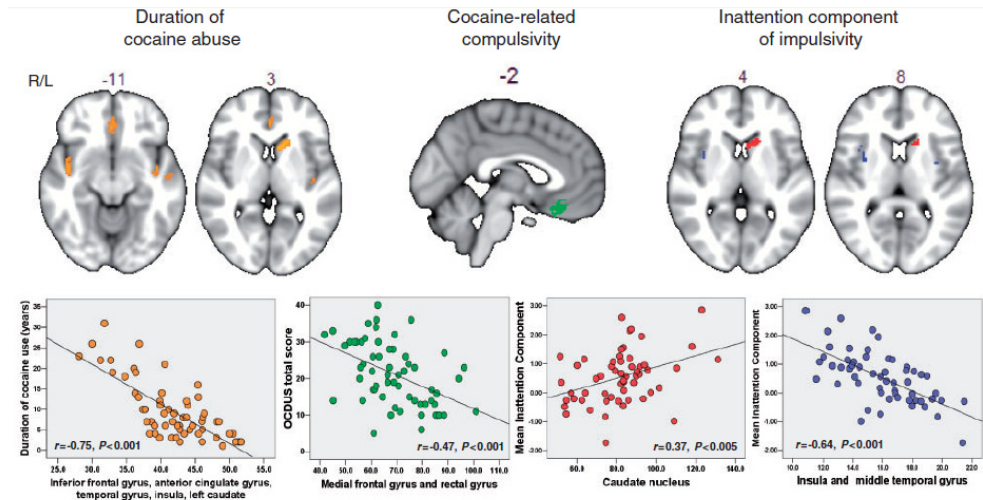

Fig. 4. Maps of brain regions. Regions where grey matter volume correlated significantly with the duration of cocaine use in drug users are indicated in orange. Regions that correlated significantly with compulsive cocaine-taking are coloured in green. Regions where grey matter volume correlated significantly with the inattention component of impulsivity in cocaine users are indicated in red (if the correlation was positive) and blue (if the correlation was negative). The scatter plots beneath each section of the brain image show the correlation between these measures and the total grey matter volume for each drug user. The numbers above each section of the image refer to its plane position (mm) relative to the origin in MNI stereotactic space. L = left; R = right (Ersche et al., 2011).

In addition, there are differences between the cocaine-dependent and healthy groups. For example, the cocaine users had higher depressive scores than the healthy people, and fewer years in formal education (11.5 compared to 12.3 years). Most of the cocaine users also had nicotine dependence (83%), some also had alcohol dependence (27%), cannabis dependence (18%) and heroin dependence (7%). These factors may also have been related to the brain differences seen, rather than just the cocaine use. Morever, Ersche et al., (2011), noted that impulsivity is a complex trait and that the measures they used would not have captured all aspects of it.

4. The signaling pathways involved in cocaine addiction

The drugs of abuse differ greatly in their chemical structure, they act on their own unique target that are mostly proteins involved in synaptic transmission, although different drugs affect different neurotransmitter systems (Nestler, E., 2004).

All addictive drugs facilitate dopamine transmission. The dopamine projection to the prefrontal cortex (PFC), nucleus accumbens (NAc) and amygdala is a primary site of pharmacological action by cocaine, as well as a site where addictive behaviors such as relapse and sensitization can be initiated (Berridge and Robinson., 1998). The regions of the prefrontal cortex most clearly tied to addiction in both neuroimaging studies in addicts and lesion/pharmacological studies in animal models of addiction (rats) are the anterior cingulate/prelimbic cortex and the ventral orbital cortex (Neisewander et al., 2000; Goldstein and Volkow., 2002; Kalivas., 2004).

The NAc is composed of two compartments termed the core and the shell (Zahm and Brog., 1992) and, although the shell is more clearly associated with dopamine-dependent reward, the core has been linked to the enduring cellular changes elicited by repeated use of addictive drugs (Di Ciano and Everitt., 2001; Kalivas and McFarland., 2003). The projections from the amygdala and prefrontal cortex to the nucleus accumbens are glutamatergic, as are the reciprocal connections between the basolateral amygdala and prefrontal cortex (figure 5). The prefrontal cortex also sends glutamatergic efferents to the dopamine cell body region in the ventral tegmental area (VTA). This circuit has primary output through co-localized γ-amino butyric acid (GABA)ergic and peptidergic neurons in the NAc that project to the ventral pallidum (PV) and ventral tegmental area (Kalivas., 2004).

The changes in the NAc, influenced by activation of dopamine receptors, are critically involved in behavioral adaptations (Marinelli and White., 2000). Natural rewards, but also drugs of abuse, increase VTA release of dopamine in downstream structures such as the NAc (Di Chiara, 2002; Schultz., 2002). However, an essential difference between natural rewards and drugs of abuse is that, over time, the dopamine response to the natural rewards, but not drugs of abuse, diminishes (Kalivas and O'Brien., 2008). Additionally, the amount of dopamine released following administration of a drug of abuse, particularly cocaine, typically exceeds what occurs following exposure to a natural reward. Thus, the repeated large release of dopamine is believed to be critical in the development of addiction, as it alters and modifies structures and their connections (Uys and LaLumiere,. 2008).
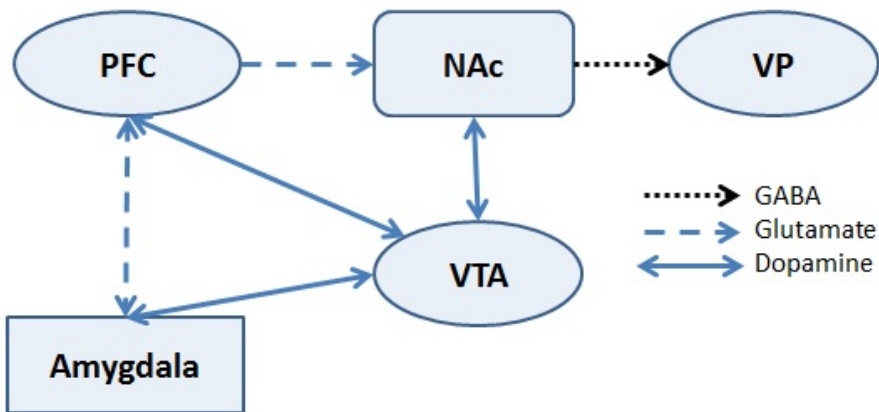

Fig. 5. The schematic diagram identify the critical structures involved in drug reward and relapse to cocaine seeking. VTA, Ventral tegmental area; PFC, Prefrontal cortex; NAc, Nucleus accumbens; VP, Ventral pallidum.

The VTA–NAc, so called mesolimbic, pathway seems to be a site where virtually all drugs of abuse converge to produce their acute reward signals. Two major mechanisms are involved: first, all drugs of abuse increase dopamine-mediated transmission in the NAc, although by very different mechanisms; second, some drugs also act directly on NAc neurons by dopamine-independent mechanisms (Everitt and Wolf., 2002).

An interesting point is the intracellular event precipitated by stimulation of dopamine receptors as a result of repeated use of cocaine. In dopamine D1 receptor stimulation of cAMP-dependent protein kinase (or PKA) and subsequent changes in protein function and gene expression in the NAc and VTA appear critical to establishing sensitization (Nestler., 2001). The most well-characterized effect of increased cAMP-dependent protein kinase activity is the induction of cAMP response element and the subsequent change in ΔFosB and cyclin-dependent kinase 5 (Nestler et al., 2001; Lu et al., 2003). In addition to the immediate consequences of dopamine receptor signaling, calcium/calmodulin and ras/mitogen-activated protein kinase activity in the ventral tegmental area are critical for the development of sensitization (figure 6). The dopamine D1 receptor stimulation–dependent activation of L-type Ca^{2+} channels and CaMKII facilitates the reinstatement of cocaine seeking by promoting the transport of GluA1-containing AMPA receptors in the NAc shell to the plasma membrane. The CaMKII activity in the NAc shell may be an essential link between dopamine and glutamate systems involved in the neuronal plasticity underlying cocaine craving and relapse (figure 6). (Wolf et al., 2004; Boehm and Malinow., 2005; Schmidt and Pierce., 2010).

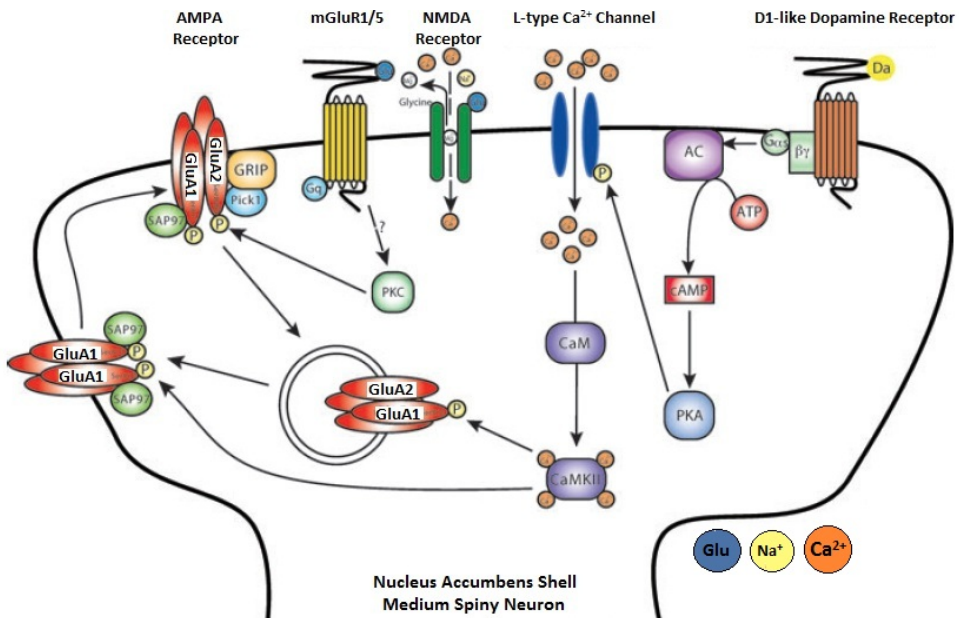Fig. 6. Pathway between NAc shell dopamine and glutamate systems, via L-type Ca^{2+} channels and Ca^{2+}/calmodulin kinase II (CaMKII), which is proposed to underlie the reinstatement of cocaine seeking. (Adapted from Schmidt and Pierce., 2010).

In contrast to dopamine, glutamate transmission appears to be a primary contributor in the majority of examples of enduring neuroplasticity in the brain, and the development and expression of cocaine addiction is no exception (Winder et al., 2002). The activation of glutamatergic efferents from the amygdala and prefrontal cortex is critical in the expression of addictive behaviors.

Cocaine indirectly influences glutamate transmission in the limbic system, including the NAc, producing persistent changes in neuronal function that can alter the behavioral effects that generate this drug. (Gass and Olive., 2008; Uys and LaLumiere., 2008; Thomas et al., 2008). Thus, maladaptive forms of neuroplasticity in the NAc contribute to cocaine-seeking behavior, and reversing these cocaine-induced neuroadaptations in glutamatergic transmission may prevent relapse of cocaine taking.

The interaction between glutamate and dopamine in VTA and NAc is rather complex, but in simplified terms, glutamatergic input to the VTA increases the activity of dopaminergic cells and enhances dopamine release in the NAc (Tzschentke., 2001). At the level of the NAc, glutamate also facilitates dopaminergic transmission, presumably by presynaptically influencing dopamine release (Floresco et al., 1998; Tzschentke and Schmidt., 2003).

5. The role of glutamate, and GABA receptors in cocaine addiction

The glutamate as neurotransmitter interacts with specific ionotropic glutamate receptors (iGluR) or metabotropic glutamate receptors (mGluR) (Dingledine et al., 1999; Cull-Candy et al., 2001). The ionotropic family of glutamate receptors consists of three subfamilies of tetrameric receptors; N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPAR), and kainate receptors. Agonist binding induces a conformation change in NMDA, AMPA, and kainate receptors that increases the probability of channel opening. Different subunit compositions of ionotropic glutamate receptors produce functionally diverse NMDA, AMPA, and kainate receptors that are expressed differently throughout the brain (Dingledine et al., 1999).

The latter are the G protein-coupled receptor. Through various G proteins, they connect to multiple second messenger systems. There are three functional groups of mGluRs (group I–III) classified from eight subtypes (mGluR1–8) (Conn and Pin., 1997). Group I mGluRs (mGluR1/5 subtypes) are positively coupled to phospholipase Cβ1 through Gαq proteins. Activation of mGluR1/5 increases phosphoinositol hydrolysis, resulting in intracellular Ca^{2+} release and protein kinase C (PKC) activation (Conn and Pin, 1997). Both group II (mGluR2/3) and group III (mGluR4/6/7/8) receptors are negatively coupled to adenylyl cyclase through Gαi/o proteins. Their activation reduces cAMP formation and inhibits protein kinase A (PKA).

Group I mGlu receptors can also couple Homer proteins through a Homer-phosphatidyl-inositol 3-kinase enhancer (PIKE) adaptor complex (Szumlinski et al., 2008). This is particularly important for mGlu receptor trafficking into and out of the synapse and also to functionally connect mGlu to iGlu receptors.

5.1 Ionotropic receptors and cocaine

The glutamate neurotransmission in the NAc core is necessary for cocaine-induced behaviors, which are regulated by AMPA receptors (Pierce et al., 1996). In addition, chronic

cocaine treatment changes iGluR's in both the PFC and NAc. In cocaine sensitized rats, there is an increase in GluN2B receptors in the NAc shell and decreased Tyr1472 phosphorylation in the NAc core with an increase in GluA1 Ser845 phosphorylation in the PFC, NAc shell and core (Zhang et al., 2007). Interestingly, glutamate receptor trafficking may be highly relevant for cocaine-induced neuroplasticity (Lau and Zukin., 2007).

Dopamine D1 receptor stimulation of rat PFC cortical neurons increases surface expression of GluA1-containing AMPA receptors through a protein kinase A-dependent mechanism (Sun et al., 2005). Cocaine self-administration increases synaptic GluA2-lacking AMPA receptors in the NAc after withdrawal (Conrad et al., 2008). Likewise when sensitized animals are re-exposed to cocaine after 10–14 days of withdrawal, both AMPAR surface expression and AMPA/NMDA ratio were shown to be decreased 24 h later (Boudreau et al., 2007; Ferrario et al., 2010; Kourrich et al., 2007; Thomas et al., 2001). GluA2-lacking AMPA receptors may therefore be a novel target for treating cocaine addiction.

The effect of repeated cocaine exposure on the cellular distribution of AMPARs is of functional significance because it has been shown that drug seeking requires AMPAR transmission in the NAc (Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001) and that enhanced AMPAR transmission in the NAc is associated with enhanced drug seeking (Anderson et al., 2008; Conrad et al., 2008; Suto et al., 2004; Wolf and Ferrario, 2010).

Carrie et al., (2011) showed effects of a single cocaine exposure in rats and the difference from those previously reported after repeated cocaine administration. They further suggested that cocaine exerts these effects by influencing neuronal circuits rather than simply stimulating NAc DA transmission.

Cocaine injection administered to rats pretreated with repeated cocaine injections results in increased glutamate release in the NAc core (McFarland et al., 2003; Pierce et al., 1996; Hotsenpiller et al., 2001). There are different neuroadaptations in the accumbens core and the accumbens shell. When cocaine is injected during withdrawal from repeated cocaine exposure, occurs that cocaine decreased presynaptic glutamate immunoreactivity in the accumbens core, but not the accumbens shell (Kozell et al., 2003, 2004). Similarly, cocaine–induced reinstatement of drug seeking was associated with increased glutamate release in the core of the nucleus accumbens, an effect that is attenuated by pharmacological inactivation of the medial prefrontal cortex (mPFC) (McFarland et al., 2003). Then, the administration of an AMPA receptor antagonist into the NAc blocked the reinstatement of cocaine seeking induced by administration of cocaine directly into the mPFC (Park et al., 2002). The activation of the glutamatergic projection from the mPFC to the NAc promotes cocaine seeking (Park et al., 2002)., a finding supported by brain imaging studies of human cocaine addicts, which demonstrate that cocaine craving is associated with metabolic activation of the mPFC (Volkow et al., 2005). These findings also demonstrate that stimulation of AMPA glutamate receptors in the NAc plays a critical role in cocaine seeking (Schmidt and Pierce., 2010).

Has been established an association (correlation) between AMPAR phosphorylation and enduring behavioral plasticity (behavioral sensitization and more significantly drug-seeking behavior), although a causal link between them remains to be proven experimentally (Mao et al., 2011). S845/S831 phosphorylation is likely to be up-regulated to increase surface AMPAR expression   thereby enhancing AMPAR transmission related to behavioral

plasticity (Boudreau and Wolf, 2005; Conrad et al., 2008). However, self-administration of cocaine induced lesser S845 phosphorylation in the striatum as compared to acute cocaine injection, establishing a tolerance of S845 phosphorylation in response to chronic cocaine (Edwards et al., 2007). This tolerance may reflect a down-regulated GluA1 function in accumbens neurons and may contribute to cocaine sensitization and cocaine-seeking behavior (Sutton et al., 2003; Bachtell et al., 2008). These imply a phosphorylation-dependent mechanism for AMPAR plasticity and drug-seeking (Mao et al., 2011).

In terms of NMDA receptors there is evidence that links post-translational modifications of glutamate receptors to excitatory synaptic plasticity and drug-seeking behavior (Di Ciano, Everitt, 2001). Generally, modification processes of striatal glutamate receptors are sensitive to addictive drugs such as cocaine.

Dopamine D2 receptors are involved in the regulation of NMDA receptor phosphorylation (Liu et al., 2006). A single dose of cocaine induced a heteroreceptor complex formation between D2 receptors and GluN2B-containing NMDA receptor in D2 receptor-bearing striatopallidal neurons. The interaction of D2 receptors with GluN2B disrupted the association of CaMKII with GluN2B, thereby reducing phosphorylation at the CaMKII-sensitive site S1303 and inhibiting NMDA receptor currents. Behaviorally, this phosphorylation, involving D2–GluN2B interaction, suppressed the inhibitory indirect pathway to promote a full motor response to cocaine. Chronic cocaine reduced GluN1 S896 phosphorylation in the rat frontal cortex at 24 h, although not 14 days after of withdrawal (Loftis and Janowsky, 2002). However, acute, repeated, and self-administration of cocaine increased GluN1 S897 phosphorylation in the rat striatum (Edwards et al., 2007). Then the fact that S897 is a sensitive site modified by cocaine can show the importance of post-translational modifications in NMDA receptor plasticity and drug craving (Mao et al., 2011; Hemby et al., 2005).

5.2 Metabotropic receptors and cocaine

An acute injection of cocaine did not alter the total accumbal expression of mGluR5 protein but was enough to reduce surface expression of mGluR5 in the nucleus accumbens, suggesting that trafficking of mGluRs plays a critical role in cocaine-induced synaptic plasticity (Fourgeaud et al., 2004). There is evidence that indicates that mGluR2/3 and mGluR5 proteins are redistributed to the synaptosomal membrane fraction after a period of extended, but not acute, forced abstinence (Ghasemzadeh et al., 2009).

In fact, mGluR2/3s have already been demonstrated to play a key role in the excessive glutamate release believed to promote drug-seeking (Kalivas, 2004). Acute and chronic cocaine treatment alter the normal function, expression or traficking of group I metabotropic receptors in the NAc of rats (Mitrano et al., 2008). A single injection of cocaine decreases the proportion of plasma membrane-bound mGluR1a in the NAc shell dendrites 45 minutes after the injection, while chronic cocaine treatment decreased mGluR1a in the NAc core dendrites. This is in contrast to acute and chronic cocaine treatment having no effect on the localization of mGluR5 receptors (Mitrano et al., 2008). Another study found a decrease in mGluR1a in the NAc shell of chronic cocaine treated rats (Ary and Szumlinski., 2007; Uys and LaLumiere., 2008). Mice lacking mGluR5 receptors do not self-administer cocaine or show an increase in locomotor activity after cocaine treatment, despite having a similar

increase in dopamine levels in the NAc as compared to wild-type mice (Chiamulera et al., 2001). Activation of the perisynaptic group II mGluR receptors, mGluR2/3, decreases presynaptic glutamate release in the NAc (Xi et al., 2002; Moran et al., 2005)

Likewise the cocaine-induced plasticity in excitatory synapses within the NAc initiates adaptive changes in neuronal ensembles that lead to drug-seeking behavior and alters subsequent physiological responses to cocaine, including increased trafficking and surface expression of AMPA receptors, during protracted withdrawal (Schmidt and Pierce., 2010).

Glutamate receptors antagonists produce undesirable side effects on neurological functions. Therefore, modulation, rather than blockade, of glutamatergic transmission would be more advantageous. Accordingly, glutamate transmission-modulating agents have emerged as possible therapeutic compounds in preclinical and clinical studies (Kalivas, 2004).

5.3 GABA in cocaine addiction

GABA is an inhibitory neurotransmitter that is found primarily in the brain. As mentioned previously, the VTA plays a role in the reinforcing effects of most drugs of abuse, including cocaine, and consists of both dopaminergic and GABAergic cell bodies along with afferent terminals containing a variety of neurotransmitters. Then GABA acts as the primary inhibitory neurotransmitter in the VTA, and the GABAergic environment in the VTA has been understudied in the realm of cocaine abuse. High GABA levels result in low levels of dopamine. However cocaine diminishes transmission through of type a GABA-A receptor on dopaminergic cells in the VTA, and stimulation of other GABA-B receptor, instead, can counteract the reinforcing properties of cocaine.

The activation of GABA-A and GABA-B receptors inhibit VTA neurons, reduce dopamine release, and reduce cocaine-induced increases in extracellular dopamine (Klitenick et al., 1992; Fadda et al., 2003). GABA-A receptors are also located on GABAergic interneurons presynaptic to dopaminergic VTA neurons, and activation of these receptors would be predicted to inhibit GABAergic interneurons, disinhibit VTA neurons, enhance dopamine release, and enhance cocaine-induced increases in extracellular dopamine (Klitenick et al., 1992; Xi and Stein, 1998). Now, given the interactions between GABA and dopaminergic systems, GABAergic ligands may be useful for modifying some of the abuse-related effects of cocaine. Then the use of an among mechanistically diverse GABA agonists, high-efficacy GABA-A modulators may be the most effective for modifying the abuse-related effects of cocaine (Barrett et al., 2005).

On the other hand, acute cocaine toxicity is frequently associated with seizures. The mechanisms underlying the convulsant effect of cocaine are not well understood. Previously, studies have shown that cocaine depresses whole-cell current evoked by gamma-aminobutyric acid (GABA) in hippocampal neurons freshly isolated from rats. Cocaine's effect was voltage-independent and concentration-dependent. Ye and Ren, (2006), suggest that cocaine induces an increase from intracellular calcium [Ca]i, which stimulates phosphatase activity and thus leads to dephosphorylation of GABA receptors. This dephosphorylation-mediated disinhibitory action may play a role in cocaine-induced convulsant states.

6. Therapeutical targets for cocaine addiction

Studying the pathways involved in cocaine addiction, it is possible to know that pharmaceutical industries are hardly working on pharmacotherapies to treat this addiction and that must be directed toward the molecular transductors of abnormalities found in cocaine users. In the present section, we´ll show some of the most used pharmacotherapies and the usual targets that are regulated for them. In general, we can say that most of those therapies have been used firstly in other pathologies and assayed in cocaine addiction according to their action mode or target.

Topiramate: is a sulphamatefructopyranose derivative, thought to antagonize a drug's rewarding effects by inhibiting mesocorticolimbic dopamine release via the gamma aminobutyric acid (GABA) activity and inhibition of glutamate function after drug intake. Through this activity, topiramate may decrease extracellular release of dopamine in the VTA projecting to the nucleus accumbens. This action may mediate drug-seeking behaviors and craving by reducing the rewarding effects associated with drug use (Johnson et al., 2004).

Disulfiram: inhibits plasma and microsomal carboxylesterases and plasma cholinesterase that inactivate cocaine systemically thereby increasing blood levels of cocaine without any cardiovascular toxicity. Another important role is that disulfiram chelates copper, and since copper is essential in the function of the dopamine beta-hydroxylase enzyme, disulfiram inhibits the conversion of dopamine to norepinephrine. Dopamine betahydroxylase inhibition by disulfiram leads to decreases in peripheral and central norepinephrine and increases in dopamine levels. This effect is believed to contribute to disulfiram's efficacy in treating cocaine addiction (McCance-Katz et al., 1998)

Ondansetron: Post-synaptic 5-HT3 receptors are located densely on the terminals of corticomesolimbic dopamine containing neurons, where they promote DA release. A primary effect of ondansetron a 5-HT3 antagonist is to decrease dopamine release, especially under suprabasal conditions in these regions (Haile et al., 2009)

Baclofen: is a GABA B receptor agonist used to reduce muscle spasticity in different neurological diseases. It is believed to modulate cocaine-induced dopamine release in the nucleus accumbens. In animal studies baclofen was found to reduce cocaine self-administration, reinstatement, and cocaine seeking behaviors in rats suggesting its potential utility as a medication for treatment of cocaine addiction. In humans, an open label study found that baclofen 20 taken three times daily significantly reduced cocaine craving in cocaine-dependent subjects. However, this trial had a sample size of 10 and did not have a placebo arm. An analysis of the same data found that baclofen significantly reduced cocaine use in the subgroup of patients with the heaviest cocaine use only (Fadda et al., 2003)

Modafinil: a functional stimulant, is FDA approved for the treatment of narcolepsy and idiopathic hypersomnia. The mechanisms underlying modafinil's therapeutic actions remain unknown. It is believed to occupy both the dopamine and norepinephrine transporters consistent with a stimulant like effect. In addition, modafinil appears to increase release of the excitatory neurotransmitter glutamate, and decrease the inhibitory neurotransmitter GABA. Modafinil is usually well tolerated, although up to 3% of patients on modafinil experienced cardiovascular side-effects such as hypertension, tachycardia, and palpitations. Because of its stimulant-like activity, modafinil was suggested and later tested as a treatment for cocaine dependence. It was believed to diminish not only the symptoms

of cocaine withdrawal, but also act as a "substitution treatment" for cocaine (Ballon and Feifel., 2006).

Naltrexone: (NTX) has long been available as an orally available antagonist at opioid receptors, with a relative selectivity for the µ-opioid receptor at lower doses. It was originally studied as a potential treatment for opiate dependence, where it seems to be effective in special cases, but not across the broad range of patients. NTX taps into known EtOH actions in a seemingly logical manner. EtOH administration leads to release of endogenous opioid peptides, and one of the downstream effects of this is to activate mesolimbic dopamine (DA) release. This in turn contributes to acute positive reinforcing properties of drugs of abuse (Kreek et al., 2002). Consistant with this chain of events, µ-receptor null-mutant mice do not self-administer EtOH (Roberts et al., 2000; Heilis and Egli., 2006).

Other medications that interact with GABA- or glutamate-mediated neuronal systems have been tried as potential treatment for cocaine dependence. While there is preclinical evidence that acamprosate can inhibit conditioned place preference to cocaine and attenuates both drug and cue-induced reinstatement of cocaine-seeking behavior there is to date, no clinical trial testing its utility in treating humans with cocaine dependence. Gabapentin is another gabanergic drug used to treat both epilepsy and neuropathic pain. Its exact pharmacological mechanism remains unclear. Gabapentin has showed some promising results in an open-label study and case series suggesting that it might have utility in the treatment of cocaine dependence. There are encouraging preclinical data that support the utility of vigabatrin as a treatment agent for cocaine dependence. Vigabatrin is another anticonvulsant that increases GABA neurotransmission but this time by inhibiting GABA transaminase. It is a drug with great potentials but needs to be tested in adequately powered placebo controlled randomized studies. Tiagabine is yet another anticonvulsant that increases GABA neurotransmission by blocking the presynaptic reuptake of GABA. In 2 randomized clinical trials involving cocaine dependent patients who were maintained on methadone, tiagabine (12-24 mg/day) was found to decrease cocaine use compared with placebo (Bowers et al., 2007; Gonzalez et al., 2003) .

Finally, the use of stimulants has been tried for the treatment of cocaine dependence under the premise of a drug substitution for a drug with slower onset formulation and less abuse liability. Methylphenidate, a dopamine and nerepinephrine reuptake inhibitor used to treat attention deficit hyperactivity disorders (ADHD) was found to be no better than placebo in the treatment of cocaine dependent patients without comorbid ADHD. However when used in a population with dual diagnosis of cocaine dependence and ADHD, results from clinical trials were mixed. While a controlled clinical trial using immediate release methylphenidate (90 mg/day) found no difference between the active drug and placebo groups, another trial using sustained release methylphenidate (60 mg/day), found significant improvement in ADHAD symptoms that were associated with decrease in cocaine use compared with placebo. Though medications such as those that facilitate gabaergic function, modulate dopaminergic function or act as an agonist replacement therapy show promise in treating cocaine dependence, there are certain drawbacks (Levin et al., 2007).

Other authors (Heilis and Egli., 2006) have organized medication used in cocaine addiction in three different groups. The medications described in past paragraphs are classified in the "first wave: currently available treatments" and "second wave: the near future". Those medications have been used in mixes between them and have shown interesting results.

Table 1 summarizes some aspects related to treatment and targets of first, and second wave medications.

Medication	Group (wave)	Target, mechanism	References
Disulfiram	First	Blocking aldehyde dehydrogenase (alcohol treatment), and dopamine beta-hydroxylase (cocaine dependence)	Carroll et al., 2004
Naltrexone (NTX)	First	Antagonist at opioid receptors	Kirchmayer et al., 2000
Acamprosate (ACM)	First	Glutamate antagonist, attenuates NMDA signaling through spermidine site and actions at metabotropic glutamate receptors	Spanagel & Zieglgansberger, 1997; Harris et al., 2002.
NTX and ACM mixed	First	Opioid receptors, NMDA receptors and metabotropic receptors	Rist et al., 2005; Spanagel & Mann, 2005.
Ondansetron	Second	Serotonin receptors	Higgins et al., 1992; Meert, 1993; Tomkins et al., 1995.
Baclofen	Second	Agonist at GABA-B receptor. Treatment when in detected additional alcohol dependence	Stromberg, 2004.
Topiramate	Second	Proposed effects: blockade of voltage dependent sodium channels, antagonism of kainite receptors and potentiation of GABA signaling through increased GABA availability	Zona et al., 1997; Gryder & Rogawski, 2003; Kaminski et al., 2004, White et al.,1997

Table 1. Medications used in cocaine dependence, showing its classification and possible mechanism (or target) of action. The main use of those medications is in alcohol dependence treatment but they have shown good results in other dependences as cocaine addiction (adapted from Heilis and Egli., 2006)

The third wave medications in cocaine addiction have been used with promising results. The development of pharmacotherapy for cocaine addiction is based on previous strategies designed to alleviate other chemical dependencies such as alcoholism and opiate addiction, focusing on the neurobiological and the behavioral bases of addiction. To date, however, no pharmacotherapy has been approved by the U.S. Food and Drug Administration for cocaine dependence, but two major classes of medications have been investigated: (1) dopaminergic agents and (2) antidepressants. Studies have been relatively brief for both types of agents and have focused on abstinence initiation rather than on relapse prevention. In addition to dopaminergic agents and antidepressants, other compounds such as calcium channel blockers, have been examined as potential treatments of cocaine dependence (figure 7) (Carrera et al., 2004)

In the first group, some dopaminergic agents have been used based on the theory that chronic cocaine use reduces the efficiency of central DA neurotransmission, several dopaminergic compounds, including amantadine, bromocriptine, mazindol, and methylphenidate, have been examined as treatments for cocaine abuse. Investigators hoped that these dopaminergic agents, which have a fast onset of action, would correct the DA dysregulation and alleviate the withdrawal symptoms that often follow cessation of stimulant use.
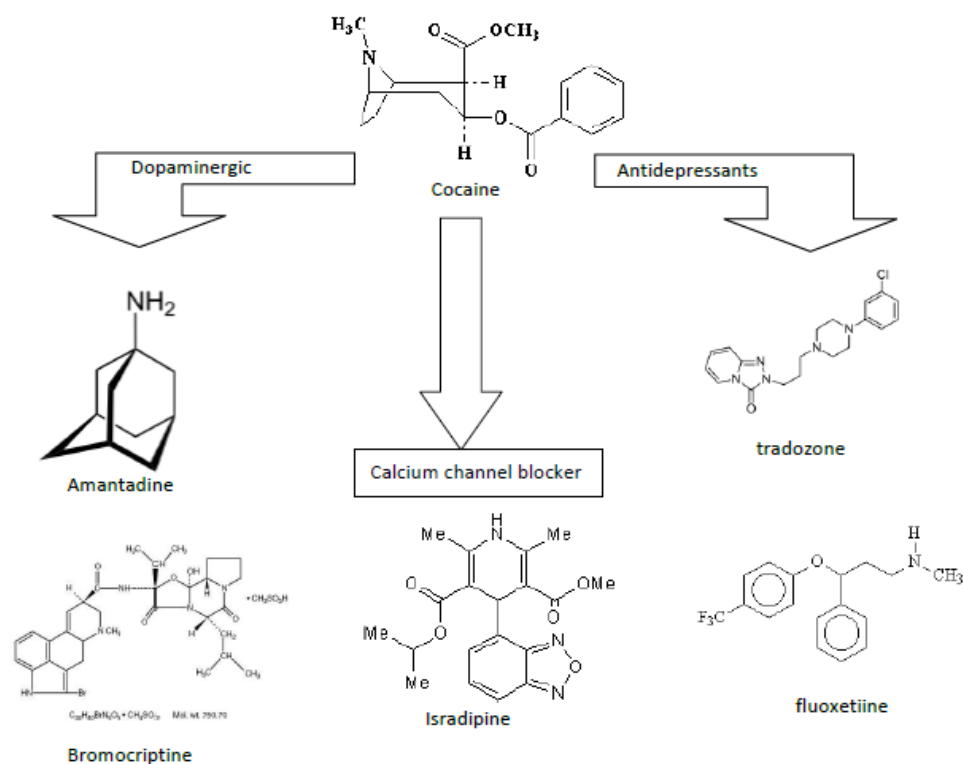

Fig. 7. Classification of medications used for cocaine addiction, based on target and mechanism of action (based on Carrera et al., 2004).

Large array of cocaine analogues and other dopamine uptake inhibitors (see Table 2) including analogues of WIN-35,065, GBR-12909, nomifensine, and benztropine have been developed in the last years. The largest class of compound studies is the class of 3-phenyltropane analogues, of which many hundreds have been made and tested. The analogues RTI-112 and PTT are in preclinical evaluation. Like cocaine, RTI-112 and PTT both have good affinity for all three monoamine transporters, but in contrast to cocaine they enter the brain slowly and are long-lasting. A number of other 3-phenyltropanes are potent and selective for the dopamine transporter relative to inhibition of serotonin and norepinephrine transporters, are long-lasting, and also enter the brain more slowly than cocaine, for example, RTI-113 and RTI-177 (Carrera et al., 2004).

The effect of inhibiting neurotransmitter uptake is to stimulate neurotransmitter receptors; thus the use of direct receptor agonists as substitute agonist medications also has been suggested. Data on dopamine receptor agonists have been extensively reviewed. Animal studies indicate that dopamine receptor agonists such as apomorphine and bromocriptine maintain self-administration in rodents.

Compound	CNS target
RTI-113, RTI-177, GBR-12909	DA uptake inhibitors (selective for DAT)
Mazindol, methyl phenidate, nomifensine, benztropine	DA uptake inhibitors (not selective)
Apomorphine, bromocriptine, SKF38393, quinpirole	DA receptor agonists and partial agonist
Desipramine	Antagonist of cocaine binding that spare DA uptake
Fluoxetine, alaproclate	5HT uptake inhibitors
Quipazine	5HT receptor agonist
Ketanserin, ritanserin, ondansetron	Calcium channel blockers

Table 2. List of some compounds that have been used as pharmacotherapy in cocaine addiction and target identified in Central Nervous System (adapted from Carrera et al., 2004)

The second class of medications used to treat cocaine dependence, antidepressants, are thought to down regulate synaptic catecholamine receptors, and this action is opposite to the presynaptic up-regulation caused by chronic stimulant use. Although antidepressants have a relatively benign side-effect profile, good patient compliance rates, and lack of abuse liability, they have a delayed onset of action ranging from 10 to 20 days. Therefore, the physician may consider beginning antidepressant treatment during early withdrawal and continuing for weeks or longer as clinically indicated. The tricyclic antidepressant desipramine has been studied most extensively as a treatment of cocaine dependence. Early studies of desipramine to treat cocaine dependence showed positive results but placebo-controlled trials have not produced impressive findings. A meta-analysis of placebo-controlled studies by Levin and Lehman showed that although desipramine did not improve retention in treatment, it did produce greater cocaine abstinence relative to placebo. However, treatment with desipramine has induced "early tricyclic jitteriness syndrome" and cocaine craving, as well as relapse to cocaine use in some patients. Therefore, desipramine as pharmacotherapy would hold serious clinical caveats. Additional studies have focused on the involvement of the 5HT3 receptor subtype in the neuropharmacology of cocaine, but the results obtained are somewhat inconsistent. Several 5HT3-selective antagonists, including MDL-72222 and ondansetron were reported to attenuate cocaine-induced locomotor activityin rodents. However, ondansetron failed to block the reinforcing or discriminative-stimulus effects of cocaine in rodents. Several other antidepressants, including fluoxetine, sertraline, and trazodone, that work predominantly through serotonergic mechanisms also have been used as pharmacotherapy for cocaine dependence. Although some reports indicated that treatment with fluoxetine reduced cocaine craving and use in cocaine-abusing heroin addicts, other investigators have not found fluoxetine to be effective in attenuating cocaine use and withdrawal symptoms. Bupropion, a "second-

generation" antidepressant, has been studied as pharmacotherapy for cocaine dependence (Heilis and Egli., 2006; Carrera et al., 2004)

Various studies suggest that L-type calcium channel blockers potentially reduce the rewarding effects of cocaine. One such compound, the L-type calcium channel blocker isradipine (Fig. 7), attenuated the cocaine induced dopamine release in the striatum of rats. Another report described isradipine-induced attenuation of condition place preference and the discriminative stimulus properties of cocaine. Also, pretreatment with isradipine resulted in a dose-dependent decrease in intravenous cocaine self-administration. Because of the antihypertensive quality of calcium channel blockers, the potential increase in cardiac output in patients with normal ventricular function could complicate their use as pharmacotherapies for cocaine abuse (Carrera et al., 2004)

Notwithstanding the impressive amount of research effort in this area, a large number of studies using dopaminergic drugs have failed to yield encouraging results. To date, no pharmacotherapeutic agent of this type used on an experimental basis has been shown effectiveness that would merit medical implementation.

7. Perspectives

The fact that GABA and glutamate are so widely present makes it likely that they will be altered during drug addiction. This fact also makes it difficult to treat addiction with drug therapy. Say that a drug affects GABA and glutamate in way that relieves craving. Because GABA and glutamate are so widely present, these drugs could produce a mess of side effects as well. If we had drugs that could selectively stimulate or block certain receptors, then we could treat addiction and avoid doing people more harm than good.

Treatment studies should continue the present emphases on (1) identifying and systematically testing pharmacological agents that may be useful in achieving abstinence from cocaine and reducing the likelihood of relapse; (2) characterizing and understanding the processes and outcomes of existing treatments by using field studies with outcomes studied over a 1-year post treatment period and longer; and (3) testing the efficacy of specific psychosocial interventions such as psychotherapies, behavioral treatments, and relapse prevention strategies. The need for theory-based treatment approaches should be recognized. Promising pharmacotherapies also should be field tested in clinical programs to understand issues related to compliance with medication regimens.

Recent efforts to discover new pharmacs have been oriented to get a vaccine for cocaine addiction. However, to improve existing treatment, there should be a systematic effort to integrate research and treatment. Research should develop and test criteria for client-treatment matching so that the most cost-effective treatments can be provided for cocaine dependent users. Additional research should focus on better understanding motivation as a factor for increasing the retention of cocaine users in treatment. This focus would include use of motivational incentives to enter and remaining treatment. There is a need to better understand the role of self-help in treating cocaine users.

Additional studies for the current cocaine vaccine are planned to confirm and extend the discussed outpatient studies, and there are ongoing developmental studies of alternative adjuvants and vaccine constructs which will likely improve the quantity and quality of

antibodies produced, as well as the proportion of high response subjects. Such results would lead to clinical application of these vaccines for in the treatment of cocaine abusers. Better vaccines or newer methods will not be the end of the game for treating substance abuse, however. The motivated cocaine addict will need other interventions such as therapy and rehabilitation programs in order to overcome this seductive addiction. Anti-drug programs in schools should be strengthened, as cocaine addiction often starts before age 20. The criminal justice system should reconsider the wholesale incarceration of cocaine users, and offer help rather than punishment. Let us hope that in the years ahead anti-cocaine vaccination will be one of numerous arrows in our therapeutic quiver to combat drug addiction (Kinsey et al., 2010).

Incorporation of technology into treatment methods is also being explored. Computer-assisted therapies may offer more consistent and convenient delivery of instruction and reinforcement in conjunction with CBT. An additional and innovative approach, to be used with a structured treatment program, is the administration of a therapeutic cocaine vaccine. The vaccine is shown to inhibit the cocaine 'high' through antibodies binding to cocaine in the circulation and inhibiting entry to the brain. However, it does not stop drug cravings. In addition, recent findings suggest that only those subjects who attain high (> 43 ug/L) IgG anticocaine antibody levels benefited from significantly reduced cocaine use. Unfortunately, only 38% of the vaccinated subjects achieved such high IgG levels. Psychosocial therapy is still essential in medication and vaccine studies because the underlying issues of the dependence and use behavior must be addressed or individuals may relapse or resort to misusing another drug. The intent of the vaccine is to immunize motivated patients as part of a comprehensive recovery program and to inhibit the reinforcing activity of cocaine and decrease the likelihood of relapse (Penberthy et al., 2010).

8. Acknowledgements

9. References

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