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Targeting glutamate homeostasis for potential treatment of nicotine dependence

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Abstract

Several studies demonstrated that impairment in glutamatergic neurotransmission is linked to drug dependence and drug-seeking behavior. Increased extracellular glutamate concentration in mesocorticolimbic regions has been observed in animals developing nicotine dependence. Changes in glutamate release might be associated with stimulatory effect of nicotinic acetylcholine receptors (nAChRs) via nicotine exposure. We and others have shown increased extracellular glutamate concentration, which was associated with downregulation of the major glutamate transporter, glutamate transporter 1 (GLT-1), in brain reward regions of animals exposed to drug abuse, including nicotine and ethanol. Importantly, studies from our laboratory and others showed that upregulation of GLT-1 expression in the mesocorticolimbic brain regions may have potential therapeutic effects in drug dependence. In this review article, we discussed the effect of antagonizing presynaptic nAChRs in glutamate release, the upregulatory effect in GLT-1 expression and the role of glutamate receptors antagonists in the treatment of nicotine dependence.

Keywords

Nicotine; nAChRs; GLT-1; xCT; iGLURs; mGluRs

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Conflict of Interest

The authors declare no conflict of interest.

1. Introduction

Nicotine dependence is one of the most preventable causes of death in the world (Jacobs et al., 1999, Doll et al., 2004). Consumption of tobacco, a product containing nicotine, leads to premature death in developing countries and in the USA (Cosin-Aguilar et al., 1995, Holford et al., 2014). It is well known that chronic nicotine consumption increases the mortality and morbidity rates in the world (Perry et al., 1984, Slotkin et al., 1997, Thun et al., 2000). Nicotine acts on nicotinic receptors, which are distributed at both pre- and post-synaptic terminals in neurons of various brain regions (Albuquerque et al., 2009), and it regulates different signaling pathways, including reward system (Watkins et al., 2000). The role of nicotine in the brain's reward neurocircuitry has been investigated extensively (Pontieri et al., 1996, Reid et al., 2000, Saellstroem Baum et al., 2006, Goriounova and Mansvelder, 2012). It has been shown that nicotine exposure is linked to dopamine and glutamate neurotransmission (Fu et al., 2000, Lambe et al., 2003, Saellstroem Baum et al., 2006, Kleijn et al., 2011). Nicotine stimulates dopaminergic neurons in the ventral tegmental area (VTA) via activation of nicotinic acetylcholine receptors (nAChRs) (Tizabi et al., 2002, Li et al., 2014). It is important to note that dopaminergic neurotransmission plays an important role in drug dependence (Fu et al., 2000, Tizabi et al., 2002, Dani, 2003). However, several studies demonstrated that glutamatergic neurotransmission is also involved in drug dependence (Cornish and Kalivas, 2000, Giorgetti et al., 2001, Christian et al., 2013). It has been reported that neuroadaptation of the glutamatergic system occurs in drug dependence (McFarland et al., 2003).

Glutamatergic projections from the prefrontal cortex (PFC) into nucleus accumbens (NAc) and ventral tegmental area (VTA) are very critical in drug dependence (Parsegian and See, 2014). In addition, dopaminergic inputs from NAc into VTA have been found to play an important role in drug dependence (Yun et al., 2004). Additionally, changes in glutamate release may affect dopamine release in the PFC and NAc (Markou, 2008) (Figure 1).

Both dopamine and glutamate release are increased by nicotine via stimulation of presynaptic nicotinic acetylcholine receptors (nAChRs) in dopaminergic and glutamatergic neurons in the mesocorticolimbic brain regions (Markou, 2008, Parikh et al., 2010) (Figure 1). Varenicline, an nAChRs partial agonist, attenuated nicotine and ethanol interactions in the mesocorticolimbic dopaminergic system in rat models (Ericson et al., 2009, Bito-Onon et al., 2011). This compound was also found to have an analgesic effect in a mouse pain model (AlSharari et al., 2012). It has been shown that α4β2 nAChRs are present in two distinct stoichiometric arrangements, (α4) 2(β2) 3 nAChRs and (α4) 3 (β2) 3 nAChRs (Moroni et al., 2006). However, it has been found that exposure to nicotine can alter the stoichiometry of α4β2 nAChRs and consequently increase its expression (Nelson et al., 2003, Vallejo et al., 2005). Furthermore, upregulation of α4β2 nAChRs has been suggested to be the mechanism of nicotine -stimulated glutamate release (Garduno et al., 2012). Additionally, several studies found that nicotine has been found to bind to α7 nAChRs and increased glutamate and calcium release (Gray et al., 1996, Wang et al., 2006). Thus, modulation of glutamate release following exposure to nicotine might be mediated through stimulation of nAChRs expressed in glutamatergic neurons. Moreover, it has been reported that nicotine applied on medial prefrontal pyramidal cells can lead to increased extracellular

glutamate concentration in rats (Lambe et al., 2003), which might be also a result of the downregulatory effect of nicotine on glutamate transporters.

Importantly, studies have demonstrated the important role of the major glutamate transporter, glutamate transporter 1 (GLT-1, its human homolog, excitatory amino acid transporter 2, EAAT2), in nicotine self-administration, nicotine dependence, nicotine withdrawal and nicotine-induced reinstatement of preference (Knackstedt et al., 2009, Alajaji et al., 2013). GLT-1 is known to regulate the majority of glutamate uptake (Danbolt, 2001). Glutamate transmission is also regulated by another glial transporter, cystine/glutamate exchanger (xCT). This transporter was also shown to play a critical role in nicotine dependence in rats and humans (Knackstedt et al., 2009). GLT-1 and xCT have suggested as targets for treatment of drug dependence, including nicotine and alcohol (Knackstedt et al., 2009, Alhaddad et al., 2014a). Therefore, it is important to find potential therapeutic compounds that upregulate GLT-1 and xCT, and consequently attenuate nicotine and drug dependence.

Additionally, several studies demonstrated the important role of glutamate receptors in attenuating nicotine dependence (Kenny et al., 2003b, Kenny et al., 2009). It is important to note that blocking glutamate receptors has been found to reduce nicotine self-administration (Kenny et al., 2003b, Sidique et al., 2012). Moreover, inhibiting glutamate receptors has been found to decrease nicotine-induced dopamine release in mesocorticolimbic area (Kenny et al., 2003b, Sidique et al., 2012).

It has been discussed extensively about the potential role of nicotine in glutamatergic system, particularly glutamate receptors (Li et al., 2014). In addition, effects of glutamate following exposure to nicotine on both dopaminergic system and medium spiny neuron (MSN) have been investigated recently (Pistillo et al., 2015). In this review article, we discussed the literature on the modulatory effect of nAChRs in glutamate release on nicotine dependence. Importantly, we further discussed the important role of GLT-1 and xCT, as well as the implications of glutamate receptors and their potential therapeutic role for the treatment of nicotine dependence.

2. Role of nicotinic acetylcholine receptors in the modulation of glutamate release

Several studies were conducted to demonstrate the role of presynaptic nAChRs in the release of glutamate following exposure to nicotine (Gray et al., 1996, Wang et al., 2006, Garduno et al., 2012). Glutamatergic terminals express presynaptic α7 nAChRs in the rat VTA and PFC (Jones and Wonnacott, 2004, Huang et al., 2014). As shown in Figure 1, glutamate release via stimulating presynaptic α7 nAChRs in glutamate terminals may have an indirect action in dopamine release by activating ionotropic glutamate receptors (iGLURs) in dopaminergic terminals (Desce et al., 1992, Fu et al., 2000, Kaiser and Wonnacott, 2000).

Studies have shown that chronic nicotine administration modulated glutamate concentration in the VTA (Changeux, 2010) and PFC (Shameem and Patel, 2012, Falasca et al., 2014). Additionally, it has been suggested that calcium influx is the main signal pathway for

releasing glutamate after acute and chronic nicotine administration at different concentrations (McGehee et al., 1995, Gray et al., 1996, Wang et al., 2006, Dougherty et al., 2008). An influx of intracellular calcium in the PFC and hippocampus in presynaptic glutamate terminals, expressing α7 nAChRs, enhanced glutamate release after both acute and chronic exposure to nicotine (McGehee et al., 1995, Gray et al., 1996, Wang et al., 2006, Dougherty et al., 2008). Furthermore, it has been reported that the association of glutamate release and calcium influx might be blocked by methyllycaconitine, α7 nicotinic receptor antagonist (Wang et al., 2006). Moreover, α-bungarotoxin irreversibly binds to α7 nAChRs and inhibits nicotine-induced increased presynaptic calcium signaling in the central nervous system (McGehee et al., 1995). Additionally, pretreatment with α-bungarotoxin blocked choline-induced glutamate release in the PFC through inhibitory binding of choline to α7 -nAChRs (Konradsson-Geuken et al., 2009). Together, these findings suggest that presynaptic α7 nAChRs in glutamatergic terminals play an important role in the release of glutamate, and consequently release of dopamine following administration of nicotine.

Several studies demonstrated the role of α4β2 nAChRs in glutamate release after exposure to nicotine (Lambe et al., 2003, Parikh et al., 2010, Garduno et al., 2012). It has been demonstrated that acute nicotine administration activated glutamatergic synaptic transmission through stimulation of presynaptic α4β2 nAChRs in the dorsal raphe nucleus (Garduno et al., 2012). Moreover, chronic nicotine exposure has been found to upregulate α4β2 nAChRs in humans (Buisson and Bertrand, 2001). A lower dose of nicotine has been able to upregulate α4β2 nAChRs as compared to either α6β2 nAChRs or α3β2 nAChRs (Walsh et al., 2008). Moreover, amplitude of glutamate release induced by nicotine or α4β2 nAChRs agonists has been revealed to be decreased in β2 nAChRs knockout animal model (Lambe et al., 2003, Parikh et al., 2010). A study was performed to determine the morphological effects of nicotine on dendritic spines of α4β2 nAChRs showed that nicotine-induced lateral enlargement in the spine heads of α4β2 nAChRs can lead to glutamatergic synaptic plasticity, since glutamate receptors antagonists blocked the nicotine-induced spine remolding effect (Oda et al., 2014). It is important to note that α4β2 nAChRs antagonist also abolished this effect, which suggests the potential role of this receptor in glutamate release. The stoichiometry of α4β2 nAChRs was found to be altered after short and long term exposure to nicotine (Nelson et al., 2003, Vallejo et al., 2005, Srinivasan et al., 2011). It is well known that the increase in assembly of α4β2 nAChRs stoichiometry can be developed by acute and chronic nicotine administrations (Nelson et al., 2003, Kuryatov et al., 2005, Vallejo et al., 2005). This effect can lead to an increase in the expression of α4β2 nAChRs. Additionally, it has been shown that the stoichiometry of α4β2 nAChRs is an important mechanism of nicotine-induced upregulation of α4β2 nAChRs (Vallejo et al., 2005, Srinivasan et al., 2011). We suggest here that the upregulatory effects of nicotine on α4β2 nAChRs may induce the release of glutamate in the mesocorticolimbic regions. Moreover, presynaptic nAChRs antagonist in the glutamatergic terminals could be effective in reducing both nicotine-induced glutamate and dopamine releases.

3. Role of glutamate transporters in nicotine dependence

Several studies found that exposure to drugs of abuse induced a marked increase in extracellular glutamate concentration in the mesocorticolimbic regions (Smith et al., 1995,

Del Arco et al., 1998, Reid et al., 2000, Williams and Steketee, 2004, Ward et al., 2009, Ding et al., 2012, Ding et al., 2013, Das et al., 2015). It has been reported that this effect can be associated with downregulation of glutamate transporters (Knackstedt et al., 2009, Changeux, 2010, Knackstedt et al., 2010, Alhaddad et al., 2014a, Alhaddad et al., 2014b). Several glutamate transporters regulate glutamate uptake in astrocytes (Su et al., 2003, Holtje et al., 2008). GLT-1 is responsible for the removal of the majority of extracellular glutamate concentration into astrocytes (Danbolt, 2001, Jensen et al., 2015). Additionally, xCT is co-expressed with GLT-1 in astrocytes regulating glutamate homeostasis [For review see (Reissner and Kalivas, 2010)]. Studies have demonstrated the potential implications of GLT-1 and xCT expression in central reward brain regions in cocaine-seeking behavior (Sari et al., 2009, Knackstedt et al., 2010). It has been revealed that GLT-1 and xCT are downregulated in NAc after cocaine exposure (Knackstedt et al., 2010). Similarly, GLT-1 and xCT were found downregulated in the NAc, amygdala and hippocampus but not in PFC in P rats exposed to ethanol as compared to ethanol naïve group (Alhaddad et al., 2014b, Aal-Aaboda et al., 2015). Importantly, it has been shown that chronic nicotine exposure can lead to downregulation of GLT-1 (Knackstedt et al., 2009). Acute exposure to nicotine increased extracellular glutamate concentration in NAc (Reid et al., 2000, Saellstroem Baum et al., 2006). A study was performed to determine the neuropharmacological cause of high extracellular glutamate concentration induced by chronic nicotine administration (Reid et al., 2000). This study found that mecamylamine and L-trans-pyrolidine-2,4 dicarboxylic acid, a non-selective glutamate transporter blocker, inhibited nicotine-induced increases in extracellular glutamate concentration in the NAc. In addition, denervation of dopamine by local injection of 6-hydroxydopamine enhanced nicotine-induced glutamate release in NAc (Reid et al., 2000). Moreover, local perfusion of artificial cerebrospinal fluid-calcium free did not affect nicotine-increased glutamate release (Reid et al., 2000). Together, this study found that nicotine-induced glutamate release in the NAc may not be calcium or dopamine dependent-related mechanisms, which suggest that glutamate transporters may have a critical role in nicotine-induced glutamate release in mesocorticolimbic regions (Reid et al., 2000).

Importantly, nicotine self-administration decreased GLT-1 and xCT expression in the NAc and VTA but not in PFC (Knackstedt et al., 2009) (Figure 2). Furthermore, reinstatement of nicotine-seeking behavior was found associated with increased extracellular glutamate concentration, decreased GLT-1 expression and increased behavioral reactions, suggesting the potential role of glutamate transporters in relapse-like nicotine seeking (Gipson et al., 2013). Recent studies from our lab and others have demonstrated the important role of glutamate transporters. GLT-1 and xCT have been suggested as key players in ethanol intake (Aal-Aaboda et al., 2015, Alasmari et al., 2015). Thus, upregulation of these transporters by ceftriaxone, a β-lactam antibiotic known to upregulate GLT-1, was associated with attenuation of relapse to ethanol and cocaine seeking (Knackstedt et al., 2010, Qrunfleh et al., 2013, Alhaddad et al., 2014a). Additionally, ceftriaxone reduced reinstatement of conditioned place preference induced by nicotine (Alajaji et al., 2013). It has been shown that ceftriaxone attenuated also tolerance developed by the analgesic effects of morphine and nicotine dependence (Rawls et al., 2010, Schroeder et al., 2011). These effects have been associated in part through upregulation of both GLT-1 and xCT

expression. In clinics, it has been shown that N-acetylcysteine, a prodrug of L-cysteine involving xCT activation, can attenuate dependence to nicotine (Knackstedt et al., 2009, Schmaal et al., 2011). Additionally, glutamate transporter 3 type (excitatory amino acid transporter 3, EAAT3) transports glutamate at post-synaptic neurons. It has been reported that EAAT3 was found to be regulated through neuronal activity, mediating other signaling pathways like phosphatidylinositol-3-kinase (PI3K) and protein kinase C (PKC) (Nieoullon et al., 2006, Yoon et al., 2014). Moreover, P13K inhibitor, and PKC inhibitor have been found to decrease EAAT3 activity (Yoon et al., 2014). Importantly, it has been found that chronic exposure to nicotine- reduced EAAT3 activity, and this effect was found to be P13K- and PKC-dependent, since P13K- and PKC activators blocked the nicotine-induced decrease in EAAT3 activity (Yoon et al., 2014). Taken together, we suggest that GLT-1, xCT and EAAT3 may play an important role in nicotine dependence.

4. Role of glutamate receptors in nicotine dependence

It has been shown extensively that ionotropic glutamate receptors (iGLURs) and metabotropic glutamate receptors (mGluRs) have a critical role in nicotine and drug dependence (Moran et al., 2005, Terry et al., 2012, Gipson et al., 2013). It is important to note that iGLURs such as N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are found in dopamine neurons in the VTA (Wang and French, 1993, Gao and Wolf, 2007). Interestingly, NMDA receptor was found to be involved in nicotine-induced dopamine release in the NAc and VTA (Fu et al., 2000, Wang et al., 2010, Salamone et al., 2014) (Figure 1). Competitive NMDA receptor antagonist, CGS 19755, administration in the VTA blocked nicotine-induced dopamine release in the NAc (Fu et al., 2000). Furthermore, it has been found that glutamate release in the VTA mediated with high doses of nicotine increased the release of dopamine in the NAc (Fu et al., 2000). Alternatively, glycine may potentiate glutamate-activated NMDA receptors and consequently stimulate [^{3}H] dopamine release in the striatum (Desce et al., 1992). It has been shown that using conditioned place preference, nicotine dependence was attenuated in mice lacking NMDA receptors in the dopaminergic axon terminals in the VTA (Wang et al., 2010). Furthermore, administration of NMDA receptor antagonists directly into the VTA inhibited nicotine-stimulated release of dopamine in the NAc (Schilstrom et al., 1998, Fu et al., 2000). Moreover, systemic administration of NMDA receptor antagonist also blocked nicotine-induced release of dopamine (Kosowski and Liljequist, 2004). It has been reported that 2-amino-5-phosphonopentanoic acid (AP-5), a competitive NMDA receptor antagonist, blocked nicotine-activated NMDA receptor and consequently reduced [^{3}H] dopamine release in rat VTA (Jin and Fredholm, 1997, Kalivas, 2000).

Alternatively, chronic nicotine self-administration increased NMDA receptor NR2A and NR2B subunits' expression in the PFC and increased AMPA receptor GluR2/GluR3 subunits' expression in the VTA (Wang et al., 2007). Moreover, the NMDA receptor NR2A subunit expression in the VTA, PFC and amygdala was found to be increased after nicotine self-administration in rat models (Liechti and Markou, 2008, Kenny et al., 2009). Studies showed that chronic nicotine self-administration upregulated NMDA receptor NR2B subunit as well as AMPA receptor GluR2 subunit in the PFC and in the amygdala as compared to control group (Kenny et al., 2009). NMDA-increased release of glutamate has been found in

cerebellar granule cells exposed to a subacute nicotine concentration (Lim et al., 2000). Furthermore, studies have shown that systemic administration or direct application of NMDA antagonists into the VTA reduced self-administration of nicotine in rats (Blokhina et al., 2005, Liechti and Markou, 2008, Kenny et al., 2009). Reinstatement to nicotine-seeking behavior can be inhibited by the NMDA receptor subunit antagonist, suggesting that glutamate neurotransmission has a crucial role in relapse to nicotine seeking (Gipson et al., 2013). Interestingly, cotinine, a metabolite of nicotine, attenuated the effects of NMDA receptor antagonist, MK-801, in rats (Terry et al., 2012).

In regards to AMPA receptors, studies demonstrated that these receptor antagonists blocked nicotine-increased dopamine release (Sziraki et al., 2002, Kosowski et al., 2004). Topiramate, a non-selective AMPA/kainate receptor antagonist, decreased the release of monoamine that is induced by nicotine in the NAc (Schiffer et al., 2001). In addition, it has been reported that the head diameter of the dendritic spine of the NAc core and AMPA to NMDA receptors ratio currents were increased within two weeks after starting nicotine self-administration in the NAc in rat model (Gipson et al., 2013). Moreover, microinjection of AMPA receptor antagonists directly into the VTA was reported to attenuate chronic nicotine and sucrose self-administration (Wang et al., 2008). However, conflicting data have been shown regarding the effects of AMPA receptor antagonists on nicotine self-administration (Wang et al., 2008, Kenny et al., 2009). Moreover, nicotine withdrawal effects have been shown to be increased precipitately in animal models injected with AMPA/kainate receptor antagonist (Kenny et al., 2003a). This suggests that AMPA/kainite receptors may play a role in nicotine dependence.

In addition to iGLURs, mGluRs have been also demonstrated to be involved in nicotine dependence (Bespalov et al., 2005, Dravolina et al., 2007, Liechti et al., 2007, Palmatier et al., 2008, Tronci et al., 2010, Tronci and Balfour, 2011, Akkus et al., 2013). Alternatively, it has been shown that mGluR5 antagonist, 6-methyl-2-(phenylethynyl)-pyridine (MPEP), decreased nicotine self-administration in rats and mice (Kenny et al., 2003b, Paterson et al., 2003, Tronci and Balfour, 2011). In addition, mGluR5 antagonist prevented relapse to nicotine-seeking behavior in rats (Tessari et al., 2004). Moreover, MPEP reduced nicotine-induced dopamine release into the NAc (Tronci and Balfour, 2011). Another study demonstrated that MPEP decreased nicotine seeking in rats (Palmatier et al., 2008). It is important to note that long-term use ex-smokers had higher mGluR5 binding as compared to recent use ex-smokers in thalamus and frontal cortex suggesting that mGluR5 is an important biomarker for nicotine dependence (Akkus et al., 2015). Furthermore, studies have demonstrated that mGluR5 or mGluR1 antagonists are able to reduce cue-induced reinstatement of nicotine self-administration in rats (Bespalov et al., 2005, Dravolina et al., 2007). In addition, nicotine self-administration decreased mGlu2/3 receptors' function in the mesocorticolimbic area (Liechti et al., 2007). It has been suggested that presynaptic inhibitory mGluR2/3 regulates extracellular glutamate concentration (Moran et al., 2005) (Figure 2). Thus, blocking mGluR2/3 inhibits the efficacy of N-acetylcystine to reduce reinstatement of cocaine self-administration in rats, suggesting that mGluR2/3 has a role in the decrease of extracellular glutamate concentration in drug dependence (Moran et al., 2005). It has been reported that systemic or microinjection of mGluR2/3 agonist, LY379268, reduced nicotine-seeking behavior (Liechti et al., 2007). Moreover, stimulation of mGluR2

by positive receptor modulator reduced nicotine self-administration (Sidique et al., 2012). We suggest here that both iGLURs and mGluRs play a critical role in nicotine dependence. For example, iGLURs and mGluR1/5 antagonists attenuated nicotine seeking (Bespalov et al., 2005, Dravolina et al., 2007). However, mGluR2/3 functions as a negative regulatory role in glutamate neurotransmission, since mGluR2/3 agonists are able to attenuate nicotine-self-administration behavior (Liechti et al., 2007, Sidique et al., 2012).

5. Conclusion

Nicotine may be able to affect excitatory and inhibitory neurotransmitters in mesocorticolimbic brain regions. Dopamine has been long standing as target for the treatment of nicotine dependence through the use of bupropion as an FDA- approved drug, which is a dopamine transporter blocker. In addition to dopamine as a target, nicotine has been studied to have modulatory effects on glutamatergic system through multiple mechanisms in the mesocorticolimbic area. Nicotine dependence may result on changes in glutamatergic transmission mediated by smoking or tobacco use. Thus, studies clearly demonstrated that chronic exposure to nicotine has been linked to increase the release of glutamate through stimulatory effect in presynaptic nAChRs located in glutamatergic axon terminals. Furthermore, upregulating GLT-1 expression, antagonizing certain glutamate receptors or antagonizing presynaptic nAChRs may have modulatory effects in glutamate transmission, and consequently lead to attenuation of nicotine dependence. These suggest that targeting glutamatergic neurotransmission through different key proteins may have potential therapeutic effect in the treatment of nicotine dependence.

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Abbreviations

GLT-1	Glutamate transporter 1
NAc	nucleus accumbens
PFC	prefrontal cortex
VTA	ventral tegmental area
nAChRs	nicotinic acetylcholine receptors
iGLURs	ionotropic glutamate receptors
NMDA	N-methyl-D-aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
MSN	Medium spiny neuron
DA	Dopamine
EAAT3	Glutamate transporter 3

PI3K	phosphatidylinositol-3-kinase
alphaPKC	alpha protein kinase C
xCT	cystine/glutamate exchanger
mGluRs	metabotropic glutamate receptors

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Highlights

- Nicotine stimulates glutamate release and calcium influx
- NMDA and AMPA receptors antagonists decrease nicotine-induced dopamine release
- GLT-1 and xCT upregulators reduce nicotine self-administration
- iGLUR and mGluR1/5 antagonists and mGluR2/3 agonist attenuate nicotine seeking

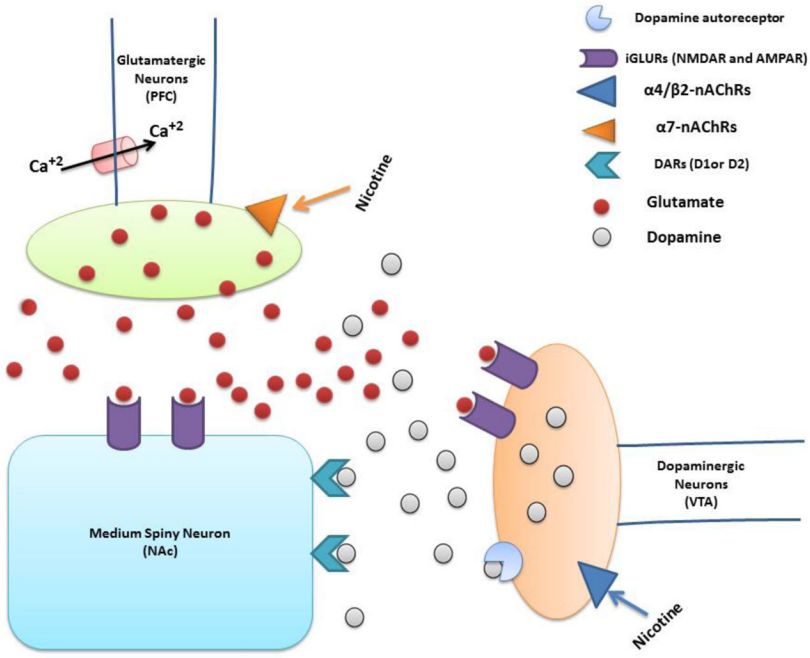

Figure 1.

Schematic diagram shows the effect of nicotine on presynaptic α7-nAChRs in glutamatergic terminals in the PFC. Glutamate released from glutamateregic neurons, binds to iGLURs in both striatal medium spiny neuron (MSN) in the NAc and dopaminergic terminals in the VTA. Glutamate activates dopamine release through stimulation of iGLURs in dopaminergic neurons. Dopamine then binds to dopamine receptor 1 (DAR1) or dopamine receptor 2 (DAR2) in the MSN, inducing dopamine actions.

Nucleus accumbens (NAc); Ventral tegmental area (VTA); Prefrontal cortex (PFC); Nicotinic acetylcholine receptors (nAChRs); Ionotropic glutamate receptors (iGLURs); N-methyl-D-aspartate (NMDA); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA); Medium spiny neuron (MSN); Dopamine receptors (DARs).

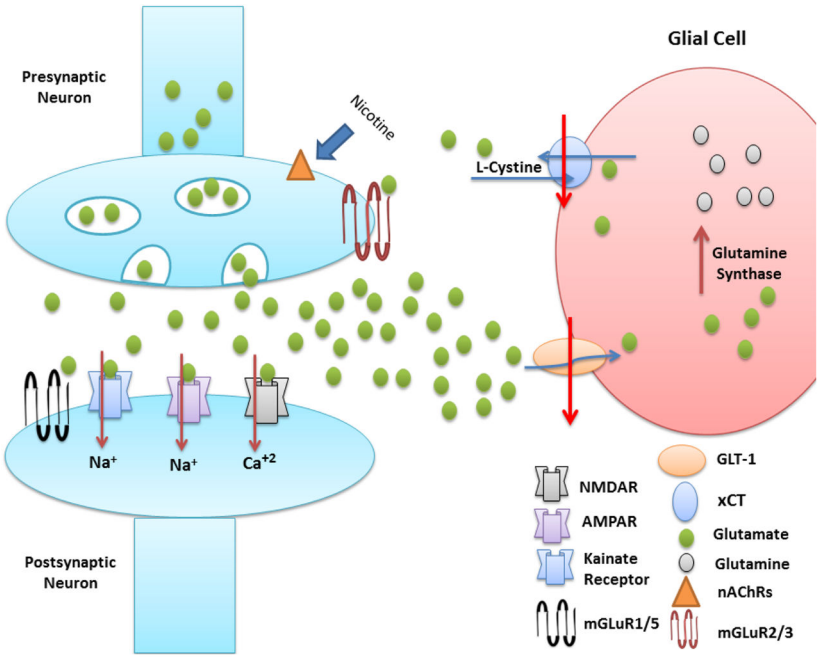

Figure 2.

Schematic diagram shows the effect of nicotine on glutamatergic system. Nicotine binds to nAChRs located at the glutamatergic terminal and elevates extracellular glutamate concentration. Moreover, decreased GLT-1 and xCT expression were associated with chronic exposure to nicotine. Glutamate is converted to glutamine by glutamine synthase enzyme in glial cells. Extracellular glutamate binds to iGLURs (NMDA and AMPA receptors) located in postsynaptic neurons. Negative feedback mechanism can occur due to binding of extracellular glutamate to mGlu2/3 receptor in presynaptic neurons of glutamatergic terminals, and consequently decreases extracellular glutamate concentration. Glutamate transporter 1 (GLT-1); cystine glutamate exchanger (xCT); Nicotinic acetylcholine receptors (nAChRs); N-methyl-D-aspartate (NMDA); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA); glutamate (GLU); metabotropic glutamate receptors (mGluRs).