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Review

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 down regulation 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.

Contents

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

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, ά-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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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 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 PFC and NAc (Markou, 2008) (Fig. 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) (Fig. 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, stimulation 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

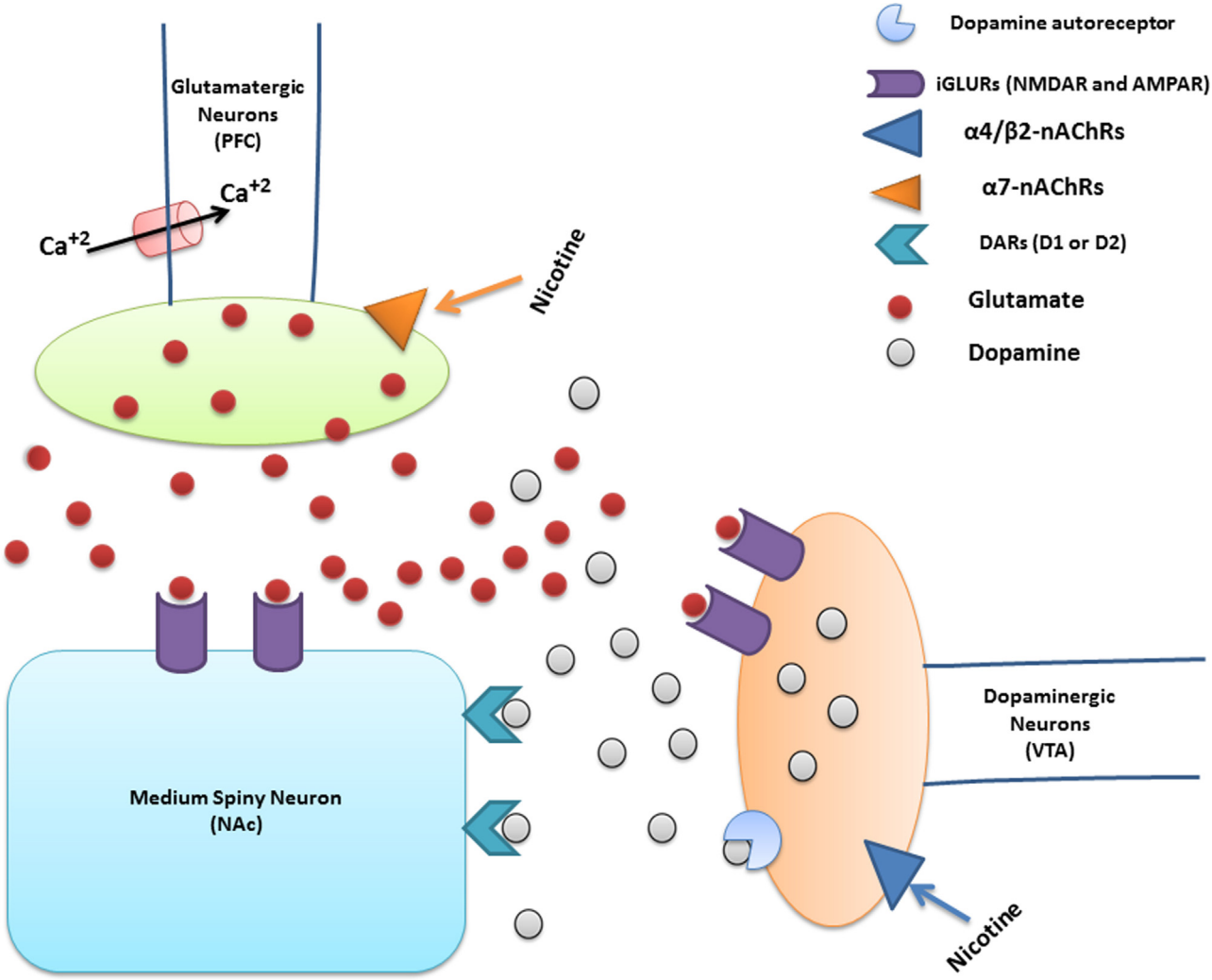

Fig. 1. Schematic diagram shows the effect of nicotine on presynaptic α7-nAChRs in glutamatergic terminals in the PFC. Glutamate released from glutamateregic neurons, binds to iGLURs in both striatal medium spiny neuron (MSN) in the NAc and dopaminergic terminals in the VTA. Glutamate activates dopamine 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).