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*Review Article*

# Nicotine Addiction: A Review

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**Abstract.** Nicotine, the major psychoactive compound in tobacco, acts as a potent addictive drug in humans. The addictive nature of nicotine leads to more than 6 million deaths a year. Evidence indicates that nicotine and other drugs of abuse act on central dopaminergic pathways and modulate their neurophysiological mechanisms. Nicotine stimulates dopaminergic pathways and the prefrontal cortex (PFC), inducing enhanced reward perception and increased cognitive function, respectively. These findings are consistent with the fact that nicotine binds to different subtypes of nicotinic acetylcholine receptors present on the neurons found in the PFC and ventral tegmental area of the midbrain. The latter, being the area most involved in addictive behaviour, projects to the limbic system, particularly the nucleus accumbens, and receives afferents from the prefrontal cortex and brainstem. Although dopaminergic pathways and nicotinic acetylcholine receptors are the protagonists of nicotine addiction, several minor pathways and their constituent receptors have been indicated as being either directly or indirectly affected by nicotine. These include serotonergic pathways and central cannabinoid receptors. Despite the scarcity of approved drugs and partial efficacy of approved treatment, insight into nicotine neurophysiological modulation has led to a better appreciation of nicotine-seeking behaviour and subsequent improved design of pharmacological and behavioural approaches to smoking cessation. Tobacco is the single most preventable cause of death in the world today. Better understanding of the neurobiological mechanisms underlying nicotine addiction will ultimately lead to more effective treatments of both nicotine dependence and nicotine rewarding effects.

**Keywords** Nicotine – Addiction – Withdrawal – Nicotinic acetylcholine receptors – Corticolimbic pathways – Smoking cessation.

## 1 Introduction

Tobacco is the single most preventable cause of death in the world today. The World Health Organisation (WHO) estimates that annually, tobacco leads to more than 6 million deaths and causes more than half a trillion American dollars of economic damage (World Health Organisation, 2013). Many types of tobacco products are consumed all over the world but the most popular form of nicotine use is through cigarette smoking. Smoking is a ubiquitous activity: more than 5,550 billion cigarettes are manufactured annually and there are approximately 1.2 billion smokers worldwide– a number expected to increase to 2 billion by 2030 (Mackay and Eriksen, 2012; World Bank, 2003). Tobacco use and its health hazards are therefore a global burden and show how tobacco is a strong motivator, despite the increased awareness of its consequential health hazards. This review will summarise knowledge of the neurophysiology of the addictive behaviour elicited by nicotine, the major psychoactive agent present in all tobacco products.

## 2 Addiction – Theories and Neurobiology

Addiction is a complex phenomenon which is still not completely understood. The traditional view is that addictive substances, such as ethanol, psychostimulants, opioids and nicotine, are all taken for two reasons: either for the pleasure the drugs elicit or to avoid the unpleasant consequences of withdrawal (World Health Organisation, 2004). Addiction is not the mere use of those drugs - it is the inability to ceasing drug intake and a compulsive pattern of drug-seeking and drug-taking behaviour that takes place at the expense of other ac-

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tivities (Robinson and Berridge, 2000). Moreover, the non-addictive, sporadic or occasional patterns of intake of an addictive drug might escalate to a frequent and compulsive one (Wellmann et al., 2004).

# 3 Manifestations of Addiction

The transition from sporadic, intermittent use to compulsive intake is a result of the interaction of the addictive substance with central neurones. This leads to long-lasting neuronal alterations of metabolism and activity, and consequently, the properties of the neuronal circuits that they constitute (Mansvelder and McGehee, 2002). This progressive change in neuronal circuitry leads to a manifestation of complex behaviours such as dependence, tolerance, sensitisation and craving (Kobb and Le Moal, 2008).

As defined in the 2010 version, 10th revision of the International Classification of Disease (ICD-10) classification of mental and behavioural disorders (WHO, 2010), substance use dependence is diagnosed whenever a case is positive on at least three of six criteria (appendix 1). Tolerance and withdrawal are two of them. Tolerance is defined as the idea that increased amounts of drug are required to achieve the same hedonic effect, or, that the same amount produces less effect. Withdrawal is the occurrence of unpleasant physical and physiological symptoms when use of the substance is reduced or discontinued (WHO, 2010). During discontinuation, relapse to substance use is known to be triggered by cues previously paired with substance use, by stress, or by presence of the drug itself (Stewart, 2000). This is elicited by uncontrollable desire for drugs, *craving* – a concept to which there is still no definite definition, due to a lack of applicability of biological models to it (Drummond et al., 2000).

In the 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association, 2013), unlike all previous versions, the criteria for substance abuse and substance dependence have been combined into one category, termed *addictions and related disorders*, and specifically expanded for each substance of abuse. Each substance use disorder is then divided into mild, moderate and severe subtypes. Moreover, whereas the DSM-IV substance abuse diagnostic criteria was requiring only 1 symptom, a DSM-V diagnosis now requires at least 2 (American Psychiatric Association, 2013).

# 4 Theories of Addiction

The mere intake of such chemicals is not equivalent to addiction. In fact, it is the properties of the chemical, together with the individual's genomic and behavioural background, which predispose an individual to addiction (Nees et al., 2013; Kendler et al., 2000). Indeed, this multifaceted phenomenon also leads to a variety of theories as to how addiction evolves.

As stated earlier, the traditional view, and the mostly intuitive explanation of addiction, is that addictive substances are taken as a result of either positive or negative reinforcement (Koob and Le Moal, 2008; World Health Organisation, 2004). Both these views have their shortcomings since it is not always the case that drugs produce such effects. For example, psychostimulants do not produce strong withdrawal syndromes, but can be highly addictive. On the contrary, anticholinergics, $\kappa$-opioid agonists and tricyclic antidepressants produce tolerance and withdrawal syndromes, but do not support compulsive patterns of use (Cote et al., 2013). Also, as stated by the pioneer of the reinforcement model (Skinner, 1953), that a stimulus reinforces a particular type of behaviour is merely an observation, and not an explanation of how the former leads to the latter.

A more holistic theory is the incentive-sensitisation theory of addiction (Robinson and Berridge, 1993). The theory states that all addictive drugs share the ability to produce long-lasting sensitisation of neural systems that subserve a subcomponent of reward – incentive salience. Drug-sensitised incentive salience causes drugs to become compulsively and enduringly wanted (which is different from *liking*), independent of drug pleasure, withdrawal, habits or memories. This phenomenon is implicit, as it can guide behaviour without a person necessarily having conscious emotion, desire, or a declarative goal (Robinson and Berridge, 2003, 2000, 1993). Robinson and Berridge (1993) also make it clear that in some cases and individuals, the positive and negative reinforcement models of addiction do apply.

# 5 Neuroanatomy of Addiction

All psychoactive drugs modulate the normal physiology of the central dopaminergic (DAergic) system (Wise, 1998) via different mechanisms. Therefore, an insight into the central DAergic pathways, particularly the nucleus accumbens-related circuitry, is paramount for the understanding of addiction.

Central dopamine (DA) is found mainly in neurons located in the ventral midbrain, especially the substantia nigra pars compacta (SNc) and the nearby ventral tegmental area (VTA). Three projection systems have been described arising from these mesencephalic nuclei: the mesostriatal (nigrostriatal), mesocortical and mesolimbic pathways (Blumenfeld, 2010). The mesostriatal pathway arises from the SNc and projects to the dorsal striatum: the caudate and the putamen. The mesocortical pathway arises mainly from the VTA and projects to the prefrontal cortex (Crossman and Neary, 2010). The roles of the mesocortical projections are to increase working memory and attention span, and the

roles for the mesostriatal pathway are to modulate intentional aspects and magnitude of locomotor activation (Blumenfeld, 2010). These pathways are affected by nicotine, but merely contribute in the reinforcement effect that it has on the human nervous system.

Finally, the mesolimbic pathway arises from the VTA and projects primarily to the nucleus accumbens (NAcc) of the ventral striatum – an area of the limbic system (Blumenfeld, 2010). Most addictive drugs, including nicotine, increase DA levels in the NAcc (Cote et al., 2013; Khalki et al., 2013; Nees et al., 2013). Evidence shows that VTA lesions and DA receptor antagonist microperfusion in the NAcc results in reduced self-administration of many addictive drugs, including nicotine (Mansvelder and McGehee, 2002). Obviously, the NAcc-related circuitry did not evolve to mediate the effects of drugs; its evolutionary intent is to use stimuli beneficial for survival, such as nutrients, water and sexual partners as natural rewards that exert motivational control over behaviour (Kelley and Berridge, 2002).

Despite the established linkage of NAcc DA levels and reward, several studies are now suggesting that this is an indirect causal relationship, since it seems that DA in the NAcc signals novelty or reward expectation, rather than reward itself (Berke and Hymann, 2000; Dani and De Biasi, 2001; DiChiara, 2000; Schultz et al., 1997). Such research correlates with the incentive-sensitisation theory of addiction (Robinson and Berridge, 1993).

# 6 The Addictive Nature of Tobacco

Although tobacco contains substances (such as nornicotine and monoamine oxidase inhibitors) which contribute to tobacco addiction, nicotine, an alkaloid, is the main psychoactive agent (Khalki et al., 2013; Sasaki, 2013). The average human plasma half-life of nicotine is approximately 2 hours, but is about 35% longer in individuals with a particular form of the gene coding for the cytochrome P450 CYP2A6 that is responsible for the primary nicotine metabolic pathway (Ande et al., 2012).

Nicotine acts as an agonist at several populations of both central and peripheral nicotinic acetylcholine receptors (this review tackles *central* receptors only). In humans, acute nicotine administration produces positive effects, including mild euphoria and mildly enhanced cognition; such subjective positive effects support intravenous self-administration behaviour in a variety of mammalian species including mice, rats and non-human primates (Markou and Peterson, 2001; Picciotto and Corrigall, 2002). Persistent nicotine use leads to tolerance that is mediated by neuroadaptation occurring in response to chronic exposure to the alkaloid, thus, within hours upon cessation of nicotine exposure, a nicotine withdrawal syndrome emerges. This syndrome is characterized by depressed mood, mild cognitive deficits and irritability (Shiffman et al., 2004).

In both rats and humans, nicotine withdrawal is characterized by both increases in somatic signs and effective changes such as reward deficits (Jonkman et al., 2007). Jonkman and colleagues (2007) also suggest that, despite no elicitation of an anxiogenic effect itself, nicotine withdrawal potentiates response to anxiogenic stimuli. On the same lines, intracranial self-stimulation (ICSS) studies on rats (Harrison et al., 2002; Johnson et al., 2008) showed that after being administered nicotine, they required lower self-applied current intensities to their reward centres to perceive pleasure. On the other hand, after withdrawal from nicotine, rats required higher intensities to perceive rewarding stimuli. Similarly, other studies showed that rats chronically treated with nicotine required higher current intensities when administered nicotinic receptor antagonists, such as dihydro-β-erythroidine (DHβE) (Watkins et al., 2000) or mecamylamine (MEC) (Hollander and Kenny, 2008). The same antagonist studies also showed that control rats (not treated with nicotine), had the same reward threshold recorded under baseline conditions after being administered DHβE.

Moreover, learning processes also contribute to nicotine dependence. For example, environmental stimuli associated with either the positive subjective effects of nicotine or the induction of nicotine withdrawal motivates nicotine seeking and eventually drug consumption (Kedikian, Faillace and Bernabeu, 2013). Studies on rats (Kenny and Markou, 2006) have shown this phenomenon by pairing flashing light with the effects of DHβE under classical conditioning processing. Those studies showed significant elevations of the reward thresholds once conditioned pairing was successful. An increased threshold was not observed in rats that had equal exposure to nicotine with unpaired light and DHβE. Such studies therefore indicate that nicotine withdrawal can be paired with environmental stimuli which alone can precipitate withdrawal syndrome.

# 7 Central Nicotinic Acetylcholine Receptors

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels comprising five membrane-spanning subunits (Changeux and Taly, 2008; Purves, 2011). Binding of the agonist is transduced into the gating of the receptor ion channel pore that is permeable to multiple cationic species ($Na^+$, $K^+$, $Ca^{2+}$) and large organic cations such as tetraethylammonium (TEA) (Fucile, 2004). 12 genes encode neuronal nAChRs sub-

units: genes CHRNA 2 to 10 encode nine isoforms of the neuronal α-subunit (α2- α10) and genes CHRNB 2 to 4 encode three isoforms of the neuronal β-subunit (β2 - β4) (Elgoyhen et al., 2001; Le Novere et al., 2002). Subunits either combine with different stoichiometries, such as two α- and three β-, or five α7-subunits to form nAChRs with distinct pharmacologic and kinetic properties (Mansvelder and McGehee, 2002).

Such distinct properties include abundancy, $Ca^{2+}$ permeability, and sensitivity to nicotine and desensitisation rates (Wonnacott et al., 2005). The heteromeric α4β2 nAChR (α4β2*) forms the majority of central nAChRs while the homomeric α7 nAChR (α7*) is the second biggest in number (Millar and Gotti, 2009). α7* are mostly permeable to $Ca^{2+}$, having fractional $Ca^{2+}$ currents of 6-12% (Fucile, 2004), comparable to $Ca^{2+}$ currents recorded in N-methyl-D-aspartate (NMDA) receptors and considerably greater than that of heteromeric (α4β2) nAChRs (2-5%) (Haghighi and Cooper, 2000). It follows, as will be later elaborated, that both types lead to increased $Ca^{2+}$ permeation: directly via α7* and indirectly by the activation of voltage-dependent calcium channels (VDCCs) through α4β2*-mediated depolarisation (Beker et al., 2003; Dajas-Bailador et al, 2002).

α4β2* have the highest affinity to nicotine since they are activated even with nicotine concentrations as low as 100-500nM (Dani et al., 2000; Millar and Gotti, 2009). Such high affinity leads to rapid desensitisation once a compatible ligand (such as ACh and nicotine) binds to this subtype (Mansvelder et al., 2002a). On the other hand, α7* are renowned for their multi-gating modes (Papke et al., 2000). α7* manifest relatively rapid desensitisation at relatively high ACh concentrations (100μM or higher) (Papke, 2006). On the other hand, α7* undergo non-desensitising activation at low ACh concentrations of 20μM (Gourlay and Benowitz, 1997; Mansvelder et al., 2002). Such phenomenon suggests that since such concentrations are present in in vivo cerebrospinal fluid (CSF), it is possible that there is a tonic activation of α7* under normal physiological conditions. Such tonicity ceases at high concentrations due to inactivation and desensitisation (Papke, 2006).

# 8 Central Location

Numerous studies show that nicotine stimulates the release of numerous neurotransmitters since nAChRs are situated in different areas of the DAergic pathways and their modulatory circuits. This section will expand on how the expression of the two main subtypes of nAChRs in the corticolimbic structures, mainly the VTA and PFC, lead to the behaviour that nicotine addiction exhibits. Modulation of mesencephalic and PFC output is ultimately due to the balance of excitatory and inhibitory inputs and the intrinsic activity of the neuronal circuits.

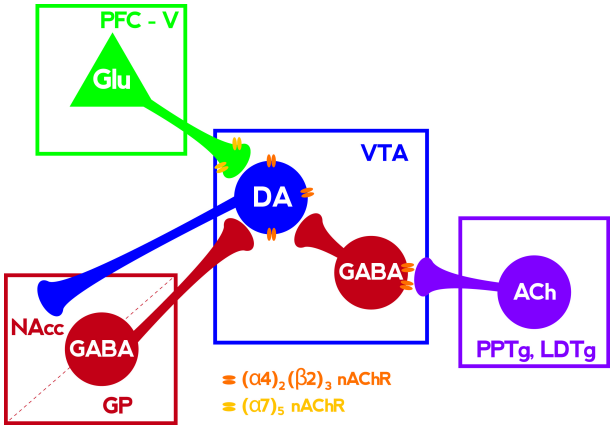


Figure 1: Simplified schematic of the main inputs and outputs of the ventral tegmental area, related nicotinic acetylcholine receptors and neurotransmitters.
The main excitatory inputs to the VTA DAergic neurons are glutamatergic projections that mainly come from layer 5 of the prefrontal cortex (PFC). Conversely, the principal inhibitory inputs to the VTA are γ-aminobutryric acid (GABA)-secreting neurons which are both local (VTA) interneurons and projections from the NAcc and the ventral pallidum. Cholinergic projections to the VTA come from two brainstem nuclei: the pedunculopontine tegmental nucleus (PPTg) and the lateral dorsal tegmental nucleus (LDTg).
Non-α7 nicotinic acetylcholine receptors (nAChRs) can excite dopamine (DA) and γ-aminobutryric acid (GABA) neurons directly, while α7 nAChRs can enhance release from glutamatergic terminals. Endogenous acetylcholine (ACh) release from brainstem cholinergic neurons contributes to the GABAergic input to VTA DA neurons.
In the presence of nicotine concentrations similar to those found in a smoker's blood, the non-α7 nicotinic acetylcholine receptors (nAChRs) desensitise rapidly, effectively inhibiting GABAergic inputs to the dopamine (DA) neurons. The α7 nAChRs will not desensitise as much, which means that glutamatergic inputs will be enhanced as the GABAergic inputs are depressed, thus leading to a net increase in excitation of the DA neurons.
*PFC prefrontal cortex, NAcc nucleus accumbens, GP globus pallidus, VTA ventral tegmental area, PPTg pedunculopontine tegmental nucleus, LDTg lateral dorsal tegmental nucleus Glu glutamate, GABA γ-aminobutryric acid, DA dopamine, ACh acetylcholine, nAChR nicotinic acetylcholine receptor.*

# 9 Ventral Tegmental Area

As shown in Fig.(1), the main excitatory inputs to the VTA DAergic neurons are glutamatergic projections that mainly come from layer 5 of the prefrontal cortex (PFC-V) (Couey et al., 2007). Conversely, the principal inhibitory inputs to the VTA are γ-aminobutryric acid (GABA)-secreting neurons which are both local (VTA) interneurons and projections from the NAcc (medium spiny neurons) and the globus pallidus (GP) (Mansvelder et al., 2002b). Cholinergic projections to the VTA come from two brainstem nuclei: the pedunculopontine tegmental nucleus (PPTg) and the lateral dorsal tegmental nucleus (LDTg) (Mansvelder and McGehee, 2002b).

There are three neuronal components in the VTA that express nAChRs: DA neurons, GABA neurons and glutamatergic presynaptic terminals that synapse on the

DA neurons (Fig.(1)) (Mansvelder and McGehee, 2002). DA neurons express messenger ribonucleic acid (mRNA) for many different nAChR subunits which give rise to at least 3 types of nAChRs, with α4β2* and α7* being the majority (Klink et al., 2001; Pidoplichko et al., 2004). GABA neurons in the VTA express nAChRs that contain α4 and β2 subunits (Mansvelder et al., 2002b) - this has been shown since GABA neurons in the VTA have been blocked by MEC at concentrations that specifically block non-α7*. Moreover, MEC microinfusion in the NAcc did not lead to a decrease in DA, thus showing that NAcc medium spiny neurons themselves express little, if any, nAChRs.

Similar VTA microinfusion studies (Shilstrom et al., 1998), this time with the NMDA receptor antagonist (2R)-amino-5-phosphonovaleric acid (APV), inhibited nicotine-induced increase of DA in the NAcc. This therefore suggests that nicotine modulates glutamate vesicle release at presynaptic glutamatergic terminals. Along the same lines, another study (Mansvelder and McGehee, 2000) showed three phenomena: 1) low-concentration nicotine infusions enhanced VTA glutamatergic transmission (showing the role of nicotine in glutamatergic release), 2) tetrodoxin (TTX), a $Na^+$ voltage-gated channel blocker, did not affect this enhancement (showing a Na+-dependent neurotransmitter release), and that 3) nAChRs are sensitive to metyhyllycaconitine (MLA), a selective α7* antagonist (showing that the $Ca^{2+}$-permeant α7* are involved). Furthermore, Jones and Wonnacott (2004) concluded that α7* are situated on vesicular glutamate transporter (vGluT) positive terminals that were devoid of vesicular cholinesterase transporter (VChat) staining. Such events therefore suggest the presence of only, or a vast majority of, α7 nAChRs on glutamatergic, not cholinergic terminals of VTA DAergic neurons (Couey et al., 2007). In conclusion, secondary to this configuration, glutamatergic projections onto the VTA exert the greatest effect of nAChRs agonists onto VTA DA neurons via axodendritic influences.

# 10 Prefrontal Cortex

The PFC receives glutamatergic inputs from the medial dorsal nucleus of the thalamus (Tmd) (Blumenfeld, 2010). Nicotine excites these thalamocortical projections, leading to an increase in glutamatergic inputs to layer 5 pyramidal neurons as well as to some in layer 6 (Couey et al., 2007). Such effects were blocked by TTX and were elicited with low concentrations of nicotine – both phenomena that indicate the presence of α4β2 nAChRs (Lambe et al., 2003). The same authors also demonstrated that nicotinic modulation of thalamocortical inputs was absent in β2-containing nAChRs knockout (KO) mice. More recently though, studies showed that both α7 and non-α7 nAChRs appear to be important in the PFC synaptosomes (Wallace and Bertrand, 2013). This occurrence is similar to that in the VTA with regards to $Ca^{2+}$ permeation, although different mechanisms are responsible for such ion flux. PFC α7* are primarily found on ryanodine positive terminals and their activation leads to calcium-induced calcium release (CICR). On the other hand, as in the VTA, activation of non- α7* increases $Ca^{2+}$ via recruitment of VDCCs (Mansvelder et al., 2009).

Although no studies have yet pinpointed the specific location of the different nAChRs subtypes, it can still be ascertained that no nAChRs are present on the pyramidal neurons (Couey, 2007). In contrast, specific GABAergic interneuron populations do express mRNA for α4, β2 and α7 subunits; the regular-spiking non-pyramidal (RSNP) interneurons and the low-threshold-spiking (LTS) interneurons (Couey, 2007). nAChRs are also expressed on the medial dorsal thalamic projection terminals (Mansvelder et al., 2009). PFC-V neurons project to various sites, including the ventral striatum (25% circa), hypothalamus (25% circa), amygdala (8%) and the VTA (4%) (Gabbott, 2005).

# 11 Nicotine and Neurophysiological Adaptations

During cigarette smoking, blood nicotine levels reach 300-500nM several minutes after the initiation of smoking and concentrations close to 250nM are sustained for 10 minutes or more (Gourlay and Benowitz, 1997). Such values disrupt the normal activity of central nAChRs which lead to modulation of normal synaptic physiology. Nicotine in the central nervous system activates the high-affinity (α4β2) nAChRs which desensitize within minutes (Dani et al., 2000). However, in vivo biochemical studies showed that a single systemic injection of nicotine enhances DA release in the NAcc for more than an hour (Di Chiara, 2000). This conclusion indicates that it is very likely such changes can be induced even after a person smokes only one cigarette.

These findings lead to the assertion that nicotine has long-lasting neurophysiological effects, which outlast short-term nAChR stimulation and desensitisation (Jiang and Role, 2008; Kawai et al, 2007). This up-regulation has previously been reported to solely involve an increase in the number of nAChR receptors (Wonnacott, 1990; Marks et al., 1992). Recent studies, although not denying an increase in receptor number, suggest that up-regulation is a change in receptor state, rather than a change in receptor number (Mansvelder and McGehee, 2002). Such nicotine-induced up-regulation, by which these long-lasting stimulatory effects ensue, are long-term potentiation (LTP) and depression (LTD) of exci-

tatory glutamatergic inputs of GABAergic transmission in both the PFC and VTA.

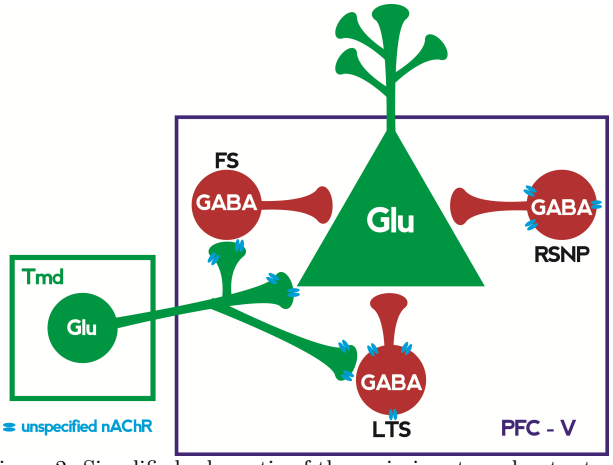


Figure 2: Simplified schematic of the main inputs and outputs of the prefrontal cortex, related nicotinic acetylcholine receptors and neurotransmitters
Nicotinic acetylcholine receptors (nAChRs) are expressed on glutamatergic thalamocortical projections and somata of GABAergic rapid-spiking non-pyramidal cells (RSNP) and low-threshold-spiking interneurons (LTS). GABAergic fast-spiking interneurons (FS) and pyramidal cells do not express nAChRs. Glutamatergic thalamocortical stimulation is increased by nicotine, eliciting an increased excitatory drive to the pyramidal neurons, LTS and FS components. RSNP cells are directly depolarised by nicotine. The net effect is therefore increased inhibition of pyramidal cells activity.
*Tmd medial dorsal nucleus of thalamus, PFC prefrontal cortex, nAChR nicotinic acetylcholine receptor, Glu glutamate, GABA γ-aminobutryric acid, LTS low-threshold-spiking interneurons, RSNP rapid-spiking non-pyramidal cells, FS fast-spiking interneurons, nAChR nicotinic acetylcholine receptor.*

## 12 Prefrontal Cortex Modulation

In normal mouse PFC, nAChRs lead to LTP by pairing the stimulation of the excitatory inputs to layer 5 pyramidal neurons with postsynaptic spikes elicited 5ms after each synaptic response (Couey, 2007). Such synaptic plasticity is brought about by the relative timing of APs in presynaptic and postsynaptic spikes and is hence referred to as spike-timing-dependent plasticity (STDP) (Mansvelder et al., 2009). In STDP, a presynaptic spike preceding a postsynaptic one by a short time window leads to LTP; the reverse order leads to LTD. This coordinated, LTP-inducing stimulus is disrupted following nicotine infusion and a depression is subsequently observed (Couey, 2007). Evidence shows that it is the increase in GABAergic input from interneurons (RSNP, fast-spiking (FS) and LTS) that brings about such depression since the nicotinic modulation of PFC plasticity was abolished by $GABA_A$ receptor antagonists (Mansvelder et al., 2009). As shown in Fig.(2), increase in GABAergic input is elicited by the nicotine-induced increase in glutamatergic inputs from the thalamic projection terminals, which synapse on pyramidal neurons and FS, both of which do not express nAChRs, and on LTS. Moreover, nicotine directly depolarises RSNPs, which do not have connections with thalamic projections, and LTS. Thus, in the PFC the overall effect of nicotine-induced nAChR activation results in a net inhibition of pyramidal cell activity.

Recalling the various PFC projections; such nicotine-induced modulation has widespread effects which to date are still controversial (Mansvelder et al., 2009). For example, Day et al. (2007) report that the nicotine-induced threshold for STDP could reduce cognitive performance. Conversely, the same study suggests that normal PFC-based stimuli during cognitive behaviour increases PFC neuronal activity and therefore makes LTP possible again. Such nicotine-dependent phenomenon could therefore enhance the signal-to-noise ratio (consequently decreasing the unwanted perturbations which all neuronal synapses manifest) and thus leading to improved cognitive performance.

## 13 Ventral Tegmental Area Modulation

4% of the PFC projections in layer 5 extend to the VTA (Gabbott, 2005). As already mentioned, nicotine is able to increase the firing rate of DA neurons. This happens both by direct nicotine stimulation on VTA DA neurons and actions on nAChRs located on GABAergic interneurons and glutamatergic terminals in the VTA (Fig.(1)).

Glutamatergic transmission onto DA neurons is enhanced by activation of presynaptic nAChRs α7*. Interestingly, cholinergic terminals are not in close proximity to glutamatergic terminals and therefore, in normal physiological conditions, ACh stimulates such terminals via a volume mode (Jones and Wonnacott, 2004). This volume mode stimulation is disrupted with nicotine and an increase in glutamatergic secretion occurs. At the same time, the various types of nAChRs on DA neurons are stimulated by the alkaloid, resulting in favourable conditions for the pre- and post-synaptic paired activation leading to LTP of glutamatergic inputs (Mansvelder and McGehee, 2000). LTP is also induced in vivo by an increased AMPA/NMDA receptor ratio (Saal et al., 2003).

Recalling that α7* are tonically active at low neurotransmitter (NT) concentrations, these receptors are not significantly desensitised by low nicotine concentrations associated with tobacco smoking (Gourlay and Benowitz, 1997; Mansvelder et al., 2002a). This ensures that nicotine-induced glutamatergic-DAergic LTP remains unaltered.

In addition to glutamate and dopamine, GABA plays another important role in VTA circuitry. GABAergic interneurons, which predominantly express α4β2 nAChRs,

undergo a transient increase of inhibitory input to the DA neurons. This effect would likely give rise to a short-lived offset of some of the excitatory effects of nicotine, an event that subsides within minutes since the high-affinity α4β2 nAChRs undergo rapid desensitisation. Also, both physiologic (Fiorillo and Williams, 2000) and ultrastructural analyses (Garzón et al., 1999) of VTA cholinergic transmission conclude that the vast majority of brainstem cholinergic projections synapse on GABAergic interneurons while very few synapse on DAergic ones.

An important question is whether VTA GABAergic depression actually contributes to nicotine addiction. In fact, there is evidence (David et al., 1997; Ikemoto et al., 1997) that rats and mice readily self-administer $GABA_A$ receptor antagonists in the VTA. Acetylcholinesterase inhibition also enhanced GABA transmission in the VTA and DA in the NAcc (Mansvelder et al., 2002b) - a phenomenon which complements the results of studies asserting that the majority of cholinergic projections end on GABA interneurons. Such evidence therefore suggests that, as shown in Fig.(2), GABAergic desensitisation will also lead to the cessation of most of the cholinergic effect on DAergic inhibition.

In summary, under normal physiological conditions α4β2* can excite DA and GABA neurons directly, while α7* enhance release from glutamatergic terminals and the somata of DA neurons. Endogenous ACh release from brainstem cholinergic neurons, apart from a scarce effect on DAergic neurons and the far-off glutamatergic terminals, mainly affects GABAergic input to VTA DA neurons. In the presence of nicotine concentrations similar to those found in the blood of a smoker, the α4β2* on GABAergic interneurons desensitize rapidly leading to the cessation of cholinergic influence on their somata and DA neuron disinhibition. α7* do not desensitise as much which means that glutamatergic inputs will be enhanced. The net effect is therefore an increase in excitation of the DA neurons via glutamatergic LTP and GABAergic depression. GABAergic depression might also help in further glutamatergic potentiation as it further favours DAergic neuron depolarisation (Mansvelder and McGehee, 2002). Such effects, which outlast nicotine exposure by hours or more, definitely contribute to our understanding on the long-lasting addictive effects of nicotine.

# 14 Others

Numerous other NTs and neuromodulators influence the activity of the VTA, including serotonin (5-HT) and endogenous opioids (Tzschentke, 2001). Seth et al. (2002), although not able to pinpoint direct evidence for presynaptic nAChRs on cortical serotonergic terminals, showed that 5-HT levels increase on nicotine exposure. Conversely, and more recently, studies conducted on rats reported that nicotine decreased serotonergic cell activity in the dorsal raphe nucleus (dRN) (Touiki et al., 2007).

There is also evidence in humans for a role of endogenous opioids in mediating nicotine dependence (Krishnan-Sarin et al., 1999). Anandamide, an endocannaboid, is indeed implicated in nicotine addiction since its levels in the forebrain and midbrain increase on chronic nicotine administration (Merritt et al., 2008).

# 15 Pharmacological Treatment for Nicotine Addiction

Although it is not the aim of this review to highlight the pharmacological approach to treat nicotine addiction, a brief outline of the current approaches and of promising novel compounds undergoing preclinical testing complement the above evidence of the mechanisms of nicotine addiction, which ultimately has effective smoking cessation as its main objective. The pharmacological treatment of nicotine addiction is divided into two approaches: substitution or eradication (Di Matteo et al., 2007). In addition, pharmacological approaches are more effective when administered during behavioural counselling (Galanti, 2008; Hurt et al., 2009; World Health Organisation, 2004). To date, varenicline is the first-line pharmacotherapy, which demonstrates the greatest efficacy when combined with behavioural support (Carson et al., 2013; West et al., 2008).

# 16 Nicotine Replacement Treatment

Substitutive treatment involves giving nicotine in various formulations in order to substitute tobacco nicotine, hence the term nicotine replacement therapy (NRT) (Hurt et al., 2009). Such treatment is effective since most adverse health effects of tobacco smoking come not from the nicotine itself, but from tars and carbon monoxide, released when tobacco products are ignited (World Health Organisation, 2004). For example, a nicotine transdermal patch provides a relatively stable, fixed dose of nicotine over a period of 16 or 24 hours (Di Matteo et al., 2007). NRT increases the long-term rates of smoking cessation and relieves craving for nicotine and withdrawal syndrome (Rigotti, 2002).

# 17 Specific Non-Nicotine Treatment

The eradicative approach involves the use of non-nicotine compounds. Varenicline, a partial nicotine agonist selectively binds to α4β2 nAChRs (Galanti, 2008). As a partial agonist it partially stimulates receptor-

mediated activity leading to the release of DA and the consequent reduction of cravings and nicotine withdrawal symptoms. Furthermore, it competes with nicotine for the nAChR binding site leading to a decrease in its reinforcing effects (Coe et al., 2005).

Varenicline is considered the best smoking cessation aid to date for long-term abstinence in the general population, with comparison to bupropion (Hurt et al., 2009; West el at., 2008) and NRT preparations (Aubin et al., 2008). Several randomised control trials (RCTs) showed that varenicline seems to be more efficient than bupropion. For example, 2 studies (Gonzales et al., 2006; Jorenby et al., 2006) showed that after a 12-week treatment regime, the drug lead to a 44% abstinence rate, versus 30% for bupropion SR and 18% for placebo. The administration of bupropion, a phenylaminoketone atypical antidepressant, was the first approved drug and is now considered with other first-line pharmacological treatments for nicotine addiction (Sutherland, 2002). The action of bupropion seems to be multifactorial, including (Hurt et al., 2009) inhibition of norepinephrine (NA) and DA reuptake (Ascher et al., 1995), nAChR antagonism (Slemmer et al., 2000). Sustained-release bupropion (bupropion SR) has been shown to be more effective and exhibits a significant dose-response effect (Hurt et al., 1997). Additionally, bupropion SR together with transdermal NRT lead to significantly higher long-term rate of abstinence from smoking (Fiore et al., 2008; Jorenby et al., 1999), since presumably NRT alleviates nicotine withdrawal symptoms and antagonists reduce the rewarding effects of smoking (Di Matteo et al., 2007).

# 18 Non-Specific Treatment

Other non-specific therapies, such as antidepressants, are also used which inhibit NA and 5-HT reuptake (Di Matteo et al., 2007). Smoking cessation has been shown to increase depressive symptoms in many individuals such that antidepressants are widely used to prevent such manifestations (Busch et al., 2011). It is also important to note that nicotine, since it increases central 5-HT levels (Seth et al, 2002), can be a form of self-medication for an underlying depression which might then be unmasked upon smoking cessation (Borelli et al., 1996).

# 19 Promising Treatment under Trial

Electronic nicotine delivery systems (ENDS) are cigarette-shaped electronic devices consisting of a battery-powered heating element to vaporize a solution containing nicotine and thence inhaled as a mist (Choi and Forster, 2013). Both nicotine and smoking-related cues appear to control cigarette craving and withdrawal symptoms, therefore ENDS may be an effective smoking cessation device (Caponnetto, 2012). Current ENDS trials are evaluating smoking reduction and abstinence effects, product preferences, and adverse effects of marketed devices (Polosa, 2011).

Mecamylamine, a non-competitive nicotinic receptor antagonist, has been evaluated for more than a decade (Kirshenbaum et al., 2011; Lundahl et al., 2000). Its non-competitive nature permits nicotine to bind, but not to impose its receptor-mediated effects. This leads to attenuation and eventually extinction of the conditioned addictive behaviour of nicotine, since tobacco consumption would not offer the same degree of motivation and reward. Such phenomenon is in fact shown by a compensatory increase in smoking to make up for the decreased nicotine-induced hedonia (Kirshenbaum et al., 2011).

A Cochrane systematic review showed that opioid antagonists, mainly naloxone, buprenorphine and naltrexone, have the potential to attenuate the rewarding effects of tobacco smoking since the central endogenous circuitry has a role in reinforcing the smoking stimulus (David et al., 2009).

Immunotherapy, also referred to as nicotine vaccination, could also be a promising solution in the near future for the sphere of smoking cessation by injecting a nicotine-like hapten, conjugated with a strong immunogen, with the consequent production of nicotine antibodies (Orson et al., 2008). Anti-nicotine antibodies would then sequestrate intravascular nicotine after tobacco smoking or ingestion (Cornuz et al., 2008). Ongoing phase III trials are expected to give rise to the first nicotine vaccines in the coming years (Aubin et al., 2011; Raupach et al., 2012).

# 20 Conclusion

The levels of consumption of tobacco are declining in developed countries but increasing in developing ones (Rigotti, 2002). Despite this fact, it is still the major preventable cause of death and quit rates remain low despite the availability of contemporary pharmacological treatments aimed at the cessation of tobacco consumption (Haas et al., 2004). Research has definitely provided much more knowledge on the neurophysiology of nicotine addiction on the human species. Despite the fact that promising results have been obtained, one also has to take into account the need for further obstacles in both neuroadaptive mechanisms and treatment to be surmounted. Some data is also obtained from experiments on animal models or in vitro settings and not from human trials. In addition, more research is needed amongst youths, who are ultimately the most vulnerable age group to addictive behaviour (PHS Guideline

Update Panel, 2008; WHO, 2008).

More circumspect research coupled with non-pharmacological approaches, public health awareness and ethico-legal measures are sure to offer better outcomes in the struggle against nicotine addiction and concomitant health hazards.

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# Appendix 1

## Criteria for Substance Dependence in ICD-10

Three or more of the following must have been experienced or exhibited together at some time during the previous year

1. a strong desire or sense of compulsion to take the substance;
2. difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
3. a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4. evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses;
5. progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
6. persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to heavy substance use, or drug-related impairment of cognitive functioning. Efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

Source: World Health Organisation (1992). The ICD-10 classification of mental and behavioural disorders: clinical description and diagnostic guidelines. Geneva: World Health Organisation. ISBN: 9241544228