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ROLE OF SEROTONIN IN RELAPSE TO NICOTINE ADDICTION: AN OVERVIEW

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ABSTRACT:

Drug addiction is regarded as the disease of the brain reward system which is considered a complex disease of the CNS. Nicotine addiction involved not only counter adaptive changes of endogenous serotonin and its receptor system, but also adaptive changes of many other neuronal transmitter systems. This study reviewed the neurobiology of nicotine addiction, the neural mechanisms of addictive drugs that can be localized to a variety of brain regions and neuronal circuitry underlying the progressive increase in nicotine relapse. Relapse can be modeled in laboratory animals by using conditioned place preference which widely is used from decades. This study also examined the role of selective serotonin reuptake inhibitors in relapse to nicotine dependence using the different inhibitors e.g. sertinazole, fluoxetine and other inhibitors significantly alter the nicotine phenomenon.

Keywords: Addiction, CNS, Serotonin, Inhibitor.

INTRODUCTION

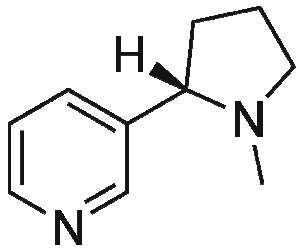
Nicotine is obtained from the leaves of tobacco, *Nicotiana tobacum* belonging to the family *Solanaceae* and has been in use for centuries. Nicotine can be smoked, chewed, or sniffed. Nicotine was isolated from leaves of tobaco in 1828 by Posselt and Reimanbasic, since then scientists started studying its effects in the brain and body. This study eventually showed that, although leaves of tobacco contain thousands of chemicals, the most active ingredient is nicotine that acts in the brain and produces addiction. Nicotine is an alkaloid (1-methyl- 2-[3-pyridyl] pyrrolidine). It is the primary component of tobacco that leads to addiction. The recent research has shown that the nicotine produces extremely powerful addiction and is atleast as strong as addictions to other drugs such as heroin and cocaine[1]. In recent years, in the youth and society the use of tobacco has taken a great roll. In fact, tobacco is the gateway drug to other drugs of abuse such as marijuana and alcohol. The notable aspect about tobacco use is that it consistently occurs early in the sequence of problem behaviors. When a young person starts smoking or using tobacco, it is a signal that he or she may get involved in other risky behaviors[1].

Pharmacokinetics of nicotine: The absorbtion of nicotine is readily to the arterial circulation from the respiratory tract, buccal and nasal mucosa, the gastrointestinal tract, skin, and also the renal tubule depending on the pH of the tissue and the nicotine delivery system. Generally about 30% of nicotine is non-ionized at physiologic pH, which allows it to readily cross cell membranes.

Pulmonary absorption of nicotine is extremely rapid, which occurs at a rate similar to that of intravenous administration. Nicotine is rapidly absorbed when cigarette is smoked, in which the (+)-isomer of nicotine is present in a proportion ranging from 3-12%, which is inhaled but negligibly absorbed when the smoke is not inhaled. Nicotine easily crosses the blood-brain barrier, reaches the brain within 7-19 seconds and reaches peak blood concentrations within 5 minutes after smoking of the cigarette. Absorption from the stomach is limited at normal intragastric pH, whereas intestinal absorption is far more efficient. Depending on the type of brand, a cigarette contains 0.5-1 mg nicotine, which is well absorbed systemically. Absorption varies according to the intensity of inhalation and the smoker's technique. Cigarette smoking produces a background level of nicotine which builds up over the day. Daytime blood and plasma levels of nicotine in

habitual smokers are routinely maintained at a constant level of approximately 0.1 μM. The initial half-life of nicotine is 7-10 minutes, and elimination half-life ranges from 1 to 4 hours. Approximately 80 to 90% metabolism of nicotine occurs in the body, mainly in the liver. Inhaled part of nicotine is metabolized by the lungs. More than 20 nicotine metabolites have been identified, the major mammalian metabolites being cotinine, nicotine-1-N-oxide and trans-3'-hydroxycotinine. Cotinine in comparison to nicotine has a more constant blood and plasma concentration of approximately 1.0 μM, and a considerably longer half-life (about 20 hours); no nicotine-like peak after smoking a cigarette can be seen[2].

Metabolites profile and the rate of metabolism do not differ between smokers and non-smokers. The concentrations of cotinine and nicotine are of course largely determined by cigarette consumption, the nicotine yield of the brand used and, to a lesser extent, by inhalation frequency. Kidney eliminates nicotine and its metabolites. Renal excretion of nicotine which is not metabolized accounts for 2-20% of total elimination, depending on urinary pH and urine flow. Nicotine and cotinine can be measured in blood, saliva and urine. The concentration in blood of nicotine is an indicator of smoking over the last few hours and the cotinine concentration reflects the amount of smoking during the last week[2].



$C_{10}H_{14}N_2$

Molecular wt. 162.24

Pharmacological effects of nicotine

Positive effects	Negative effects
Analgesia	Addiction
Antipsychotic effect	Emesis
Anxiolysis	Hypertension
Cognitive enhancement	Hypothermia
Dilatation of cerebral vessels	Respiratory failure
Neuroprotection	Seizures

Nicotine addiction: Drug addiction is generally regarded as the disease of the brain rewzard system. Addiction is considered a complex disease of the CNS, characterized by compulsive uncontrolled craving for a drug; it's seeking and striving to get it at all cost, and its use despite obvious, serious health and life threatening consequences[3,4]. Mainly three large

functional system of brain: arousal, reward and cognition system are involved in the development of drug addiction and drug seeking behavior[4]. The development of addiction and emergence of craving is most probably connected with direct disturbance of one large functional brain system, the reward system, while indirectly it also impairs remaining system- arousal system, especially its part related to emotions and cognition system[5].

Nicotine signalling: pharmacology and anatomy: Nicotine acts on endogenous nAChRs that are found throughout the central nervous system and peripheral nervous systems in almost all vertebrate and invertebrate species. The nAChRs are pentameric receptor complexes that serve as ligand-gated ion channels. So far, 12 different neuronal nAChR subunits have been identified: α2–α10 and β2–β4. The nAChR receptors form different combinations of α- and β-subunits. However, the α7–α9 subunits can also form homomeric nAChRs[6,7].

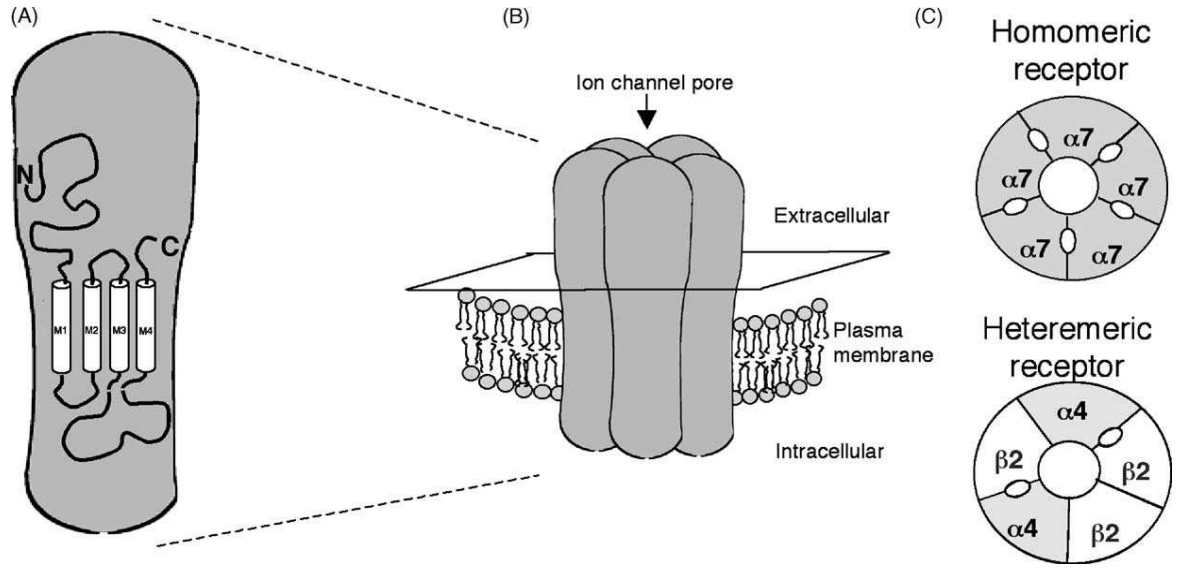


Fig.1: Molecular structure of nicotinic acetylcholine receptors[8].

Although the precise molecular structure of nAChRs is not known, they are believed to be pentameric ion channels. Each nAChR is composed of five subunits arranged in either homomeric or heteromeric complexes of α- or β-subunit arrangements. Different subunit combinations confer unique functional properties to the ubiquitously distributed nAChRs throughout the brain. The schematic on the right shows the transmembrane topology of a single nAChR subunit. Neurons within the VTA have a wide variety of nAChRs and it can activate both the DA and GABA neurons Of the VTA. The nAChR receptor profiles that are associated with these DA and GABA neurons differ considerably, and

these differences might have important functional consequences for nicotine signaling in the mesolimbic system[8,9].

Role of serotonin: Most of the previous studies in this area involved the use of various treatments that induce generalized increases or decreases in brain 5-HT function. These include indirect agonists or lesioning of 5-HT pathways induced by the selective serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT). 5-HT1A receptors are located postsynaptically on 5-HT cell bodies as well as in the dorsal and median raphe nuclei, where they function as autoreceptors. Only a few studies have examined the effects of 5-HT1A receptor agonists on drug self-administration, with inconclusive results. In rats, a moderately high dose of the prototypic 5-HT1A receptor agonist 8-OHDPAT (8-hydroxy-2-(di-n-propylamino) tetralin) (0.5 mg/ kg) reduced responding for cocaine on a fixed ratio schedule[10.]

5-HT: From the dorsal raphe nuclei, the cell bodies of the 5-HT system lies, a dense projection runs to the midbrain dopaminergic areas and these fibres form connections with both principal and secondary neurons[11]. 5-HT receptors have been classified into three subclasses, 5-HT1, 5-HT2 and 5-HT3 receptors and the ventral tegmental area is relatively rich in 5-HT receptors, in particular 5-HT1B receptors[11,12]. Based on in vivo experiments, it was hypothesised that serotonergic projections provide a tonic inhibitory control of principal neurons, mediated by 5-HT2C receptors[13]. The fact that 5-HTselective reuptake inhibitors reduce the activity of principal neurons in the ventral tegmental area is in line with this hypothesis.

A number of other different drugs of abuse, including cocaine, amphetamine methylenedioxy metamphetamine and ethanol have been shown to interact with 5-HT systems. Besides blocking the transporter of dopamine cocaine also blocks the 5-HT transporter, thereby increasing the level of 5-HT in the ventral tegmental area[14].

Neurobiological Mechanisms Underpinning Nicotine Dependence: This effect of tobacco smoking or chronic nicotine administration may reflect reduction in the concentration of 5-HT because smoking is associated with selective increase in the density of 5 HT**1A** receptors in this area. There are certain evidences evidence that hippocampus receives serotonergic innervation from the median raphe nucleus. Suppression of 5-HT release in hippocampus brings about anxiolytic response to nicotine when given locally by microinjection into the dorsal hippocampus. The effects of nicotine on 5-HT are difficult to dissociate from those on

dopamine neurons. Increased exposure to stressful stimuli is likely to raise the desire to smoke. The effects of nicotine withdrawal on dopamine release in the brain may exacerbate by the exposure to stressful stimuli and may underlie the role of stress as a factor in tobacco smoking, as well as the role of nicotine on reducing the effects by acting on 5-HT neurons within the hippocampus. Currently, there is little evidence for the involvement of the serotonergic system in the positive reinforcing effects of nicotine, but there is some evidence that this system may be involved in the negative reinforcing effects of nicotine withdrawal[1].

Dopaminergic System: The Ascending Mesolimbic and Mesocortical Pathways

Neuroanatomy:

Major ascending DA-ergic pathways originate from cell bodies in the brainstem, mainly in the substantia nigra pars compacta (SNc, A9 area) and the VTA (A10 area).

Nigrostriatal pathway:

The neurons from the SNc project through the internal capsule mainly to the striatum, thus forming the nigrostriatal DA-ergic system (Figure 1), which controls motor behavior and muscle tonus.

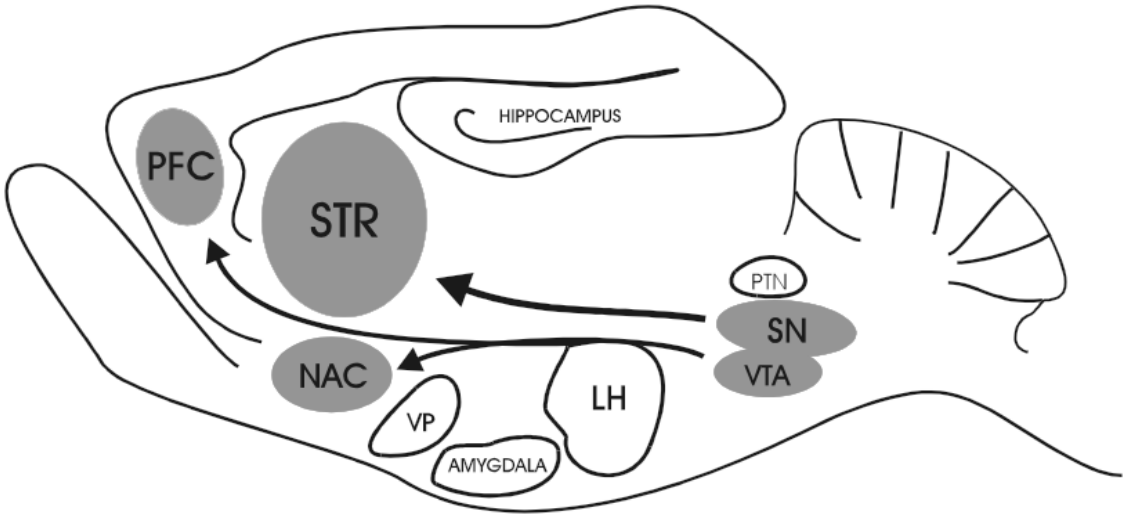


Fig. 2: Presentation of a sagittal rat brain section illustrating the nigrostriatal dopaminergic pathway (arrow from the substantia nigra to the striatum), and the mesolimbic and mesocortical dopaminergic pathways (arrows from the ventral tegmental area to the nucleus accumbens or prefrontal cortex, respectively)[15].
(SN: *substantia nigra*, STR: *striatum*, NAC*: nucleus accumbens*, VTA: *ventral tegmental area*, PFC: *prefrontal cortex*, LH: *lateral hypothalamus*, VP: *ventral pallidum*, PTN: *pedunculopontine tegmental nucleus*).

Mesolimbic pathway: The mesolimbic DA-ergic system consists of neurons which originate from the VTA and travel through the medial forebrain bundle, innervate the NAC, olfactory tubercle, and other limbic area such as the amygdala, hippocampus and septum (Figure 2). The mesolimbic system plays a key role in the

control of motivation, emotion, and motor behavior. The system is also important in mediating the rewarding properties of abused drugs. The NAC receives the strongest projections of the neurons from the VTA. Anatomically the NAC consists of subterritories, of these the ventromedial shell and dorsolateral core appear to be dominant. The shell, that receives afferents from subcortical and brainstem structures, exhibits greater neuroanatomical diversity than the core. The shell sends outputs signal to the core via the feed-forward striatopallido-thalamocortico-striatal pathway, but it also strongly innervates the lateral preoptico-lateral hypothalamic continuum and VTA[14]. Both the shell and the core area appear to be incorporated in reward-related behavior, yet they may subserve different roles[15].

Mesocortical pathway: The neurons forming the mesocortical DA-ergic system emerges from the VTA, and they travel to cortical areas including the PFC, the entorhinal and cingulate cortices. This particular brain system is involved in control of higher cognitive functions. The PFC has also been attracted in drug-reward chronic intake of an abused drug and is suggested to produce DA- ergic hypofunction in the PFC that should underlie impulsivity and loss of control of drug- seeking behavior[15].

Other pathways: In addition to these major a systems, there are also other DA-ergic systems that are shorter in length, such as the tuberoinfundibular DA-ergic system connecting the pituitary gland and the median eminence of the hypothalamus, but they are probably not so intensively involved in mediating the rewarding properties of abused drugs[14,15].

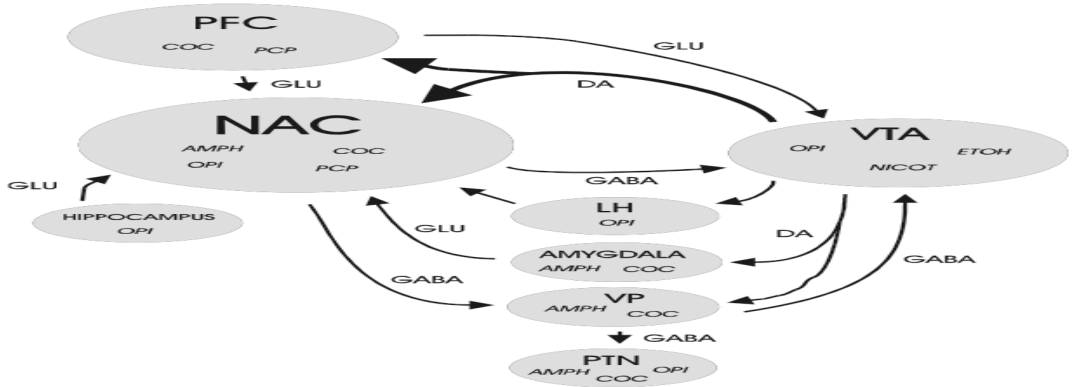


Fig. 3: Simplified schematic presentation of reward-related brain areas, and their interconnections of different neurotransmitters[15].

Abbreviation of a drug of abuse within a brain area indicates the involvement of the brain area in mediating the drug's rewarding properties. NAC: nucleus accumbens, VTA: ventral tegmental area, PFC: prefrontal cortex, LH: lateral hypothalamus, VP: ventral pallidum, PTN: pedunculopontine tegmental nucleus. DA: dopamine, GABA: ç-aminobutyric acid, GLU: glutamate. COC: cocaine, AMPH: amphetamine, OPI: opiates, ETOH: ethanol, NICOT: nicotine, PCP: phencyclidine.

CONCLUSION

The activity of the main output of the mesolimbic dopamine system, namely the dopaminergic output from principal neurons in the ventral tegmental area projecting to the nucleus accumbens, depends on a number of factors. First of all, excitatory and inhibitory inputs onto these principal neurons influence their activity. These inputs can be regulated by neuromodulatory neurotransmitters, which can also directly affect the activity of the principal neurons. Furthermore, inhibitory input from local secondary interneurons will affect the activity of principal neurons. These secondary neurons in turn also receive excitatory and inhibitory input that can be regulated. Neuromodulatory neurotransmitters can also affect the activity of secondary neurons and thus indirectly influence the activity of principal neurons. Taken together the sum of inhibitory and excitatory input to the principal neuron, combined with the intrinsic properties, regulates the output of the principal neuron. The effect of modulatory neurotransmitters depends on what component of the ventral tegmental area is affected. Another aspect of neurotransmission that modulates the output of the ventral tegmental area is activity-dependent synaptic plasticity, which is sensitive to drugs of abuse. Drugs of abuse induce long-term potentiation of glutamatergic input onto principal cells in the ventral tegmental area, thereby increasing the output of the ventral tegmental area. In conclusion, the reviewed in vitro data can explain some of the results from in vivo experiments by showing that neurotransmitter systems affect certain targets in the ventral tegmental area. Some of the neurotransmitters have multiple actions on cells and neurotransmission in the ventral tegmental area, which may account for some of the paradoxical results found in vivo. In addition, these data can be used to guide future research in which specific modulation of a specific target can be investigated.

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