

Smoking and Schizophrenia: Where is the Biological Connection?

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SUMMARY:

Objective: Patients with psychiatric disorders have a higher incidence of smoking than the general population. In particular, the rate of smoking among patients with schizophrenia has been found to be between two and three times greater than the general population in western countries. This paper reviews the biological factors that might be contributing to the high rate of smoking among patients with schizophrenia and examines the interaction between nicotine and the neurobiological disturbances observed in schizophrenia.

Method: Papers assessing the possible biological causes of smoking in patients with schizophrenia and the physiological effects of nicotine were reviewed following a search using the key words "nicotine, schizophrenia, smoking, and cigarette" in PubMed, Turk Medline, and the Turkish Psychiatric Index.

Results: Studies conducted in humans and animals show that nicotine can directly increase dopaminergic transmission in the central nervous system, enhance cognitive performance, and improve sensory gating deficits observed in patients with schizophrenia. Moreover, smoking diminishes the efficacy of most antipsychotic drugs via increased hepatic metabolism.

Conclusion: Studies in the literature suggest a link between the physiological effects of nicotine and the neurobiological disturbances in schizophrenia. Disturbances in cholinergic transmission may be responsible for some symptoms of schizophrenia. The harmful effects of smoking vastly outweigh any possible benefits, but, nevertheless, further investigation may lead to important insights regarding the etiology of schizophrenia, at the molecular level.

Key Words: Smoking, nicotine, schizophrenia, dopamine, nicotinic acetylcholine receptor

INTRODUCTION

Tobacco use has long been one of the most widespread habits throughout history. Smoking cigarettes is the most common way in which people now consume tobacco. Since the 1970's, smoking has been recognized as an important public health problem because of the high mortality and morbidity associated with its use. There are more than 4,000 chemicals in cigarette smoke, which are known to be directly toxic to cells and damaging to cell structure, as well as to cause cancer (Benowitz, 1996; Goodman, 1995).

It's significantly more frequent for people who smoke cigarettes to have oral, nose, and throat cancer due to inhalation of the smoke than it is among those who do not smoke (Beratis et al., 2001, Chou et al., 2004, Fagerstrom and Hughes, 2002). In the USA, the rate of smoking decreased from 44% of the total population in 1964 to 27% in 1991. Although this ratio decreased still further to 22.5% in 2002, it still is not yet at a desirable level (Mendez and Warner, 2004). This rate is at about 30% less than the European rate. In Turkey the current smoking rate was found to be approximately 43% (WHO, 1997): 60% in Istanbul (Ögel et al., 2003), 22% among high school students (Ögel et al. 2001), 32% among university students (Akvardar et al., 2003), and 59% among nurses (Dilbaz and Apaydin, 2002). Diagnosis of nicotine addiction, according to DSM-IV criteria (American Psychiatric Association 1994), has been found to be about 3-17% among students at Turkish universities (Akvardar et al., 2003; Çilli and Kaya, 2003).

CIGARETTES

Europeans were introduced to tobacco by the Native Americans. Tobacco leaves have been used by

means of chewing for a very long time; however, it is not clear when tobacco was first smoked. At the beginning of the 20th century, the practice of rolling tobacco with paper resulted in an increase in its use (Goodman, 1995). Although a book that showed the connection between cigarettes and cancer was published as early as 1889 by Saint John's Hospital, cigarettes were very cheap, in fact they were even sometimes free, but after World War II, many of the dangers posed by tobacco use began to be widely realized and soon were published (Benowitz 1996, Goodman 1995). Currently, there are anti-smoking campaigns in many countries throughout the world. Chronic smoking causes ventricular and sulcal atrophy (Longstreth et al. 2001), hypointense lesions of the periventricular gray matter (Tsushima et al., 2002; Longstreth et al., 2000) and diminishes volumes of gray matter in the prefrontal cortex, anterior cingulate cortex, and cerebellum (Brody et al., 2004). Despite all the damaging effects of cigarettes, clarification of the biological processes underlying excessive smoking among people who have schizophrenia might help to better understand the neurobiology of schizophrenia at the molecular level.

Nicotine

In 1512, the tobacco plant was brought to Portugal, where it was first used by means of sniffing the pulverized leaves of the plant for the purpose of relieving migraine headaches, and its use in Europe was limited to this country until 1559. In 1560, Jean Nicot brought tobacco as a wedding gift for the royal family in Paris. Later, in 1570, the tobacco plant was formally named *Nicotiana tabacum*, in his honor (Goodman, 1995; Hesse, 2002). As a result of extensive research focused on smoking addiction, nicotine ($C_{10}H_{14}N_2$), an alkaloid, was found to be both the primary psychoactive and addictive compound in tobacco. In 1828, nicotine was isolated from nicotinic acid, which is commonly known as vitamin B or niacin. It was first synthesized in the laboratory in 1904 (Figure 1). Nicotine has a molecular weight of 162.23 kDa and its full name is 3-(1-Methyl-2-pyrrolidiny) pyridine. In small amounts, nicotine acts as a mild stimulant of the central nervous system, however in its pure form, it is highly poisonous and is even used as an insecticide (Goodman, 1995; Hesse, 2002). Very low concentrations of nicotine in the blood can be enough to result in nicotine dependence, and smoking cigarettes is more than suf-

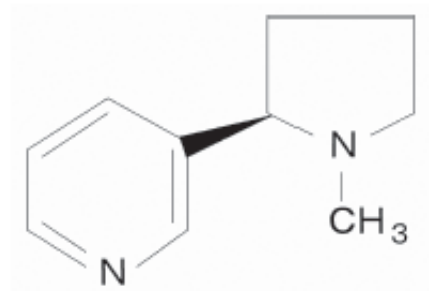
ficient to deliver nicotine in these concentrations. By smoking cigarettes, nicotine is delivered to the brain in 7 seconds, and it reaches the rest of the body within 15-20 seconds (Goodman, 1995). It is important for a smoker to develop a tolerance for the effects and side effects of nicotine (not clear). Habitual smokers develop a tolerance to certain side effects, such as dizziness and nausea, however no tolerance is ever developed to other side effects, such as high blood pressure or tremors in the hands (Kalivas and Stewart, 1991; Picciotto et al., 1998). Nicotine acts on the same neurochemical system that amphetamines and cocaine do and nicotine addiction develops quickly; for this reason nicotine addiction is categorized as substance abuse in DSM-IV (American Psychiatric Association 1994).

Both positive and negative reinforcement is important in nicotine addiction. The positive reinforcement involves a mild euphoria and increased attention and work performance. At the neurochemical level, nicotine addiction seems to be related to the stimulation of dopaminergic neurons in the ventral tegmental area (VTA) by nicotine (Corrigall et al., 1992; Pontieri et al., 1996; Uhl, 1999; Wise and Gardner, 2002). This hypothesis is supported by the fact that in the presence of lesions of the mesolimbic pathway or microinfusion of nicotine antagonists into the VTA, a decrease in nicotine addiction results (Corrigall et al., 1994). A nicotine concentration of just 0.1-0.5 μM in the blood can stimulate the VTA neurons of a smoker. Constant stimulation of the VTA neurons by nicotine will result in a permanent tolerance, and this can explain why smokers soon lose the pleasurable effects of nicotine after the first cigarette (Dani and Heinemann, 1996; Pontieri et al., 1996; Uhl, 1999).

Nicotine Receptors

Nicotine acts on the central nervous system via nicotinic acetylcholine receptors (nAChRs). Due to advancements in the laboratory over the last 15 years, which make studying nAChRs easier, there is now more research being done on this subject. Research from the fields of electrophysiology, pharmacology, and genetics has produced great insights into both the characteristics and structure of nAChRs. There are two types of cholinergic receptors: muscarinic (mAChRs) and nicotinic acetylcholine (nAChRs) that are related to the affinity of the natural alkaloids, muscarine

FIGURE 1. Chemical Structure of Nicotine.



and nicotine. nAChRs belong to the ion channel receptor family, which also includes GABA-A, 5-HT₃, and glycine. Neuronal nAChRs have a heterologic pentamer structure. In the mouse brain, the subunits of nAChRs were found to be in different areas of the brain, such as the hippocampus, the substantia nigra, the VTA, the interpeduncular nucleus, the dorsal motor nucleus of the vagus, the pineal gland, and the nucleus piriformis lateralis (Changeux et al., 1998; Salas et al., 2003; Wise and Gardner, 2002). nAChRs might be effective in the widespread inhibition of behavior paradigms. Here, the mechanism is similar to that of GABA neurotransmitters. In the brain, nAChRs are also present on the GABAergic interneurons. In both human and rodent tissues, nicotine has been shown to stimulate the release of GABA (Leonard et al., 2001; Salas et al., 2003; Wise and Gardner, 2002).

Cigarette Smoking and Schizophrenia

It is widely known that there is a higher rate of smoking among people who have psychiatric diseases than among the rest of the population, and this is especially true among those with schizophrenia (Breslau et al., 2004; Chou et al., 2004; Çilli and Kaya, 2003; Leonard et al., 2001; Mihailescu and Drucker-Colin, 2000; Poirier et al., 2002). According to data collected in the U.S.A. in 2001, it is estimated that 30% of smokers have a psychiatric disease (Chou et al., 2004). In the USA and Europe, the smoking rate has been found to be about 52-59% in both psychiatric inpatients and outpatients (Hughes et al., 1986; Poirier et al., 2002). The smoking rate among psychiatric inpatients in general is 70-88%, which is almost the same rate as that of inpatients with schizophrenia, in particular (75-85%) (de Leon et al., 1995; de Leon et al., 2002). In general, the rate of cigarette smoking among schizophrenia patients is 50-90% (Chou, 2004; Hughes et al., 1986; O'Farrell et al.,

1983; Poirier et al., 2002; Ziedonis and George, 1997). In Turkey, these rates are relatively similar, since the rate of smoking among all psychiatric outpatients is 29%, but among schizophrenics this rate is between 45% (Yıldız and Özcan, 2000) and 50% (Uzun et al., 2003). When researchers analyzed this data, the smoking rate among schizophrenics in both Turkey and Japan was not found to be significantly higher than the rate found in the general population of these two countries (Mori et al., 2003; Uzun et al., 2003; Yıldız and Özcan, 2000). However, there are some studies in Turkey, which have shown that the rate of smoking among schizophrenics is significantly higher than that of the general population. A multi-site study, which looked at 382 patients, found that the rate of cigarette smoking among schizophrenics was 54.2%. Another study found that the rate among both inpatient and outpatient schizophrenics was 57.5-69.4% (Alptekin et al., 2002; Akvardar et al., 2001; Üçok et al., 2001).

According to an age comparison, the rate of death due to respiratory and circulatory system diseases is approximately two times higher among schizophrenics than in control groups (Allebeck and Wistedt, 1986; Brown et al., 2000; Buda et al., 1988; Mortensen and Juel, 1993). Interestingly, in a recently published cohort study, which included 50,078 subjects and spanned 26 years, cigarette smoking was found to be an independent factor in the onset of schizophrenia and it was also found to be a protective factor for schizophrenia (Zammit et al., 2003).

Although it is not clear whether there is a difference in the prevalence rate of cigarette smoking between subgroups of schizophrenics, some studies suggest that this rate is higher (76-77%) within the paranoid subtype of schizophrenia (Beratis et al., 2001; Poirier et al., 2002).

People who have schizophrenia prefer to smoke cigarettes, which contain a higher amount of both nicotine and tar, and smoke the cigarette completely, right up to the filter (Lohr and Flynn, 1992; O'Farrell et al., 1983). This habit is evidenced in these individuals by a yellowish coloration of the fingernails and cigarette burns on the hands.

Although smoking in this manner is generally attributed to either forgetfulness or cognitive failure due to psychosis, it has been thought that this tendency might be explained in terms of an addic-

tion and reinforcement, since there is a very high concentration of nicotine built up near the end of a smoked cigarette (O'Farrell et al., 1983).

Effects of nicotine on the central nervous system

Clinical experience and laboratory research have both shown that nAChRs play a role in complex functions of the brain, such as memory, attention, and cognition (Leonard et al., 2001; Rezvani and Levin, 2001). Additionally, it has been reported that nAChRs might be important in the pathogenesis of a number of psychiatric and neurological diseases, such as Parkinson's disease, Alzheimer's disease, and autosomal dominant nocturnal frontal lobe epilepsy (Newhouse et al., 2001; Newhouse et al., 2004). Furthermore, the high rate of smoking observed among people with schizophrenia, attention deficit hyperactivity disorder, or depression is described as a form of self-medication by some authors (Araki et al., 2002; Leonard et al., 2001; Mihailescu and Drucker-Colin, 2000). According to the literature, there are three neurobiological hypotheses to explain the related symptoms of smoking among schizophrenics: (1) Interaction between smoking and the monoaminergic system, especially the dopaminergic system, (2) effects of nicotine on sensory gating, and (3) cognitive functions.

Smoking and the dopaminergic system

It is believed that cigarettes may provide a form of protection against the symptoms of the extrapyramidal system (EPS) because smoking results in a decreased antipsychotic level in the blood and also because nicotine stimulates stronger central dopaminergic transmission. In some studies, which provide support for this hypothesis, it has been shown that schizophrenics who smoke require higher dosages of their daily antipsychotic medications (de Leon et al., 2002; Jann et al., 1986; Lohr and Flynn, 1992; Salokangas et al., 1997; Sandyk and Kay, 1991). This need for increased levels of antipsychotic drugs has been explained by hydrocarbons due to smoking increasing the effectiveness of liver microsomal enzymes, which metabolizes the antipsychotics, and increasing of the clearance rate (Benowitz, 1996; Dalack et al., 1998; Ziedonis and George, 1997). Increase in the efficacy of the microsomal enzyme system, CYP1A2, is prominent among cigarette smokers (Bozikas et al., 2004). This enzyme is primarily responsible for

metabolizing haloperidol, but it is also known to metabolize phenothiazine, clozapine, and olanzapine, as well. Zdanis et al. (1994) showed that patients who smoke cigarettes require the equivalent of 590 mg/day of chlorpromazine, while patients who do not smoke cigarettes require the equivalent of 375 mg/day of chlorpromazine. Therefore, it may be necessary to adjust the dosages of drugs administered to patients who smoke. Nicotine is thought to affect the release of dopamine in the mesolimbic pathway as well as cause the stimulation of glutaminergic neurons in the prefrontal cortex, and therefore, it increases the effectiveness of glutamate and dopamine in the basal ganglia (Wise and Gardner, 2002). As a result of this, nicotine acts to alleviate the negative symptoms of schizophrenia, but it may also increase the positive symptoms. Atypical antipsychotics, which are accepted as being more effective against schizophrenia's negative symptoms, are more effective than typical antipsychotics for quitting smoking (McEvoy et al., 1999). Nicotine increases dopaminergic transmission in the mesolimbic pathway, which includes the nucleus accumbens and the VTA, and therefore, it stimulates the mechanism of reward, which in turn causes the smoker to continually seek nicotine (Corrigall et al., 1992).

Parkinson's disease is characterized by muscle rigidity, tremors, and bradykinesia. Perry et al. (1995) have shown that the concentration of nAChRs in the pars compact of the substantia nigra and in the laterodorsal tegmental nucleus is 70% and 50% lower, respectively, in patients with Parkinson's disease. This data prompted researchers to think that nAChRs can act as an indicator for the severity of the neuropathology in Parkinson's disease. It was shown that there was a major recovery in patients who developed Parkinson's disease after having had encephalitis when nicotine was injected subcutaneously (Mihailescu and Drucker-Colin, 2000). Fagerstrom et al. (1994) found that among nonsmoking patients who had Parkinson's disease, the use of nicotine, via either a patch or gum delivery system, helped to ease the rigidity, tremors, disorganized thoughts, and symptoms of depression associated with this disease. The positive effects of nicotine on Parkinson's disease seem to be because: (1) It increases the amount of dopamine released in the substantia nigra, (2) it inhibits the MAO-B enzyme, and (3) it stimulates dopaminergic effectiveness in the mesolimbic pathway. It has been thought that this data can

partially explain why among schizophrenics who take classic antipsychotic drugs there is a higher rate of cigarette smoking, since cigarettes can reduce the negative effects of classic antipsychotics on the musculoskeletal system (Lyon, 1999). This is supported by the fact that there is an up-regulation of dopamine 1 and 2 receptor mRNA's in the caudate, putamen, nucleus accumbens, and olfactory tubercle of animals passively exposed to cigarette smoke, or that had nicotine directly injected (Bahk et al., 2002). Moreover, there is debate as to whether or not nicotine can have a protective effect against the onset of Parkinson's disease. In some case-control studies, it has been shown that the risk for the onset of Parkinson's disease among patients who don't smoke cigarettes is half that of patients who do smoke. In another study however, it was reported that patients who smoke cigarettes have a 20-70% lower risk for Parkinson's disease than those who don't smoke (Baron, 1986). This epidemiological data supports the study of Janson et al. (1989), which showed that chronic nicotine administration has protective effects against both mechanical and chemical damage of the central dopaminergic neurons.

According to some studies, which used PET (Positron Emission Tomography), the amount of the dopamine-metabolizing enzyme, MAO-B, is 40% lower in the brains of smokers than in the brains of nonsmokers. This fact might explain the mechanism by which nicotine has both anti-depressant and antiparkinsonian effects, as the basic function of this enzyme is to metabolize dopamine. Similarly, in the brains of smokers, MOA-A activity was found to be 28% less than in nonsmokers and ex-smokers (Fowler et al., 1996; Fowler et al., 1998; Volkow et al., 1999), however, inhibition of both enzymes returns after quitting smoking. These results can help explain how nicotine bands are beneficial in helping to improve the mood state of nonsmokers with major depression (Salin-Pascual and Drucker-Colin, 1998) and also why there is such a high prevalence of cigarette smoking observed among people with depression (Covey et al., 1997). Also, these observations are concordant with findings that nicotine produces certain physiological effects, which can augment serotonergic transmission, such as increasing the rate of firing of the serotonergic neurons in the dorsal rafe of the mouse brain in a dose dependent manner, providing mood remission, and inhibiting REM (Mihailescu et al., 1998; Vazquez et al., 1996).

Nicotine and sensory gating

Many studies have suggested that schizophrenic patients primarily have a defect in their neuronal nicotinergeric system, and this defect is believed to be responsible for the abnormality of their sensory processing. This defect, therefore, can lead to abnormal sensory gating, which means that during the process of receiving, filtering, and comprehending stimuli there may be an impairment (Dalack et al., 1998). People who do not have schizophrenia display inhibited auditory excitation (P50) to the second of two successive stimuli that are exactly the same, whereas among schizophrenic patients, there is a failure to inhibit the second stimuli (Adler et al., 1993; Lyon, 1999). This means that individuals with schizophrenia have abnormal sensory gating, which is an inability to filter auditory sounds. Cigarette smoking can temporarily reduce this gating deficit (Adler et al., 1993). This data is also important because of the fact that it is never observed in healthy individuals and therefore, may be specific to the disease. P50 abnormality was found to be more frequent among first-degree relatives of schizophrenic patients than among healthy controls. This condition is autosomal dominant and related to the 13th-14th loci of the 15th chromosome, which contains the α -7 nAChR subunit (Freedman et al., 2001). Researchers have assumed that this abnormality was related to the auditory hallucinations and inability to filter other disturbing stimulants. Electrophysiological data shows that abnormal sensory gating in schizophrenia is related to nAChRs, which have an error on the α -7 subunit, resulting in long and abnormal insensitivity to stimuli (Griffith et al., 1998). In the other supporting study, it was shown that there is a relationship between decreased hippocampal volume, lower numbers of nAChRs that contain the α -7 subunit, and inheritance of P50 abnormality in schizophrenic patients (Freedman et al., 1997). In another study however, no significant difference was found between α -7 nicotinic cholinergic receptors in schizophrenic patients and controls (Lai et al., 2001). In addition to these electrophysiological abnormalities, other specific dysfunctions such as sustaining attention and processing sensory stimuli might be related to nAChRs in schizophrenic patients (Adler et al., 1998). For example, it has been known for years that anomalies in smooth pursuing eye movements are observed more frequently in schizophrenic patients and their

first degree relatives than in controls (Leonard et al., 2001; Olincy et al., 2003). It is believed that nicotine experimentally normalizes the anomaly of smooth pursuing eye movements by augmenting the cholinergic innervation of the ventrolateral geniculate and pediculopontine nuclei, which are responsible for directing the basic function of eye movement. Smoking cigarettes also normalizes the dysfunction of saccadic eye movements in schizophrenic patients (Olincy et al., 1998; Olincy et al., 2003). In the human brain, this normalizing mechanism (Freedman et al., 1993) might be the stimulation of nAChRs, which are on GABAergic interneurons and is shown by the nicotine-caused discharge of GABA in both human and animal tissues (Alkondon et al., 1997; Mac-Dermott et al., 1999). Furthermore, in a double blind study, nicotine was found to be significantly more effective than placebo at normalizing the rate of error in the antisaccadic eye movements of schizophrenics when administered in a dose-dependent manner using nicotine gum (Larrison-Faucher et al., 2004).

Nicotine and Cognitive Functions

When looked at from the angle of smoking cigarettes and recovery of cognitive deficit, there are studies showing that nicotine may be effective at attenuating the symptoms of schizophrenia, such as anxiety, apathy, and difficulty in maintaining focus. In a study done on mice, treatment with typical and atypical antipsychotics disrupted the sustained attention span, but it was restored in 1-2 weeks with the use of nicotine (Rezvani and Levin, 2004). In a study of 88 schizophrenic outpatients, 55% of whom were smokers, a significant relationship was found between daily cigarette consumption and the cognitive function component of PANSS (Positive and Negative Syndrome Scale) (conceptual disorganization, orientation disorder, difficulty in abstract thinking, poor attention, mannerisms, and posturing) among the patients who smoked (Taiminen et al., 1998). The researchers tried to explain this data by showing that cigarette smoking increases dopaminergic activity in the frontal cortex. In a double blind study, which showed the effect of nicotine on cognitive dysfunction due to schizophrenia and haloperidol treatment among schizophrenic patients, it was shown that cognitive performance among schizophrenic patients 3 hours after being administered a nicotine band was significantly higher than in

those patients who received a placebo (Levin et al., 1996). Some other studies have also lent support to the relationship between the positive effects of nicotine on cognitive performance and dopamine release, since these positive effects were shown to be inhibited by D1/D2 receptor blockers (Martin-Ruiz et al., 2003).

It has been known for a long time that the hippocampus plays a role in maintaining both attention and memory functions. In rats, during a spatial memory task, it has been shown that there are significantly more acetylcholine receptors than in the controls (Stancampiano et al., 1999). Nicotine both enhances synaptic transmission in the hippocampus (Gray et al., 1996) and induces long-lasting potentiation in hippocampus neurons (Hamid et al., 1997). Cholinergic neurons in both the medial septum and the diagonal band send fibers to the hippocampus via the fimbria-fornix, and the presence of nAChRs is very high in the hippocampus (Changeux et al., 1998; Salas et al., 2003; Schwartz, 1986). This data has suggested that the hippocampus is an important area for observing the positive effects of nicotine on memory. In the hippocampus of deceased Schizophrenic patients, the number of nAChRs was found to be significantly lower than the number of those found in controls, and this demonstrates that this receptor and its system are very important during the disease's progression (Freedman et al., 1995). In some PET studies, it has been shown that nicotine, when given as a nasal spray, has caused metabolic changes in certain neuroanatomical areas, such as the left inferior frontal gyrus, left posterior cingulate, right anterior thalamus, and right amygdala, where a strong association with cognitive processing is observed (Domino et al., 2000; Zubieta et al., 2001). In these studies, nicotine increased the neuronal metabolism, especially in the inferior frontal gyrus, left posterior cingulate, and right thalamus, whereas it decreased metabolism in the left anterior temporal cortex and right amygdala. The most important support regarding the effects of nicotine on cognitive performance comes from studies on individuals who have Alzheimer's disease. The studies, which used agonists (Jones et al., 1992; Newhouse et al., 1988; Newhouse et al., 1993; Newhouse et al. 1996; Sahakian and Coull, 1994; Wilson et al., 1995) and antagonists (Newhouse et al., 1992; Newhouse et al., 1993; Newhouse et al., 1994) of nAChRs in Alzheimer's disease, have emphasized the importance of nAChRs in the cog-

nitive process. Despite the fact that subcutaneous or intravenous applications of nicotine have positive effects on extended visual attention, reaction time, and perception in individuals with Alzheimer's disease, they have no positive effects on the short-term visual or auditory perceptive memory (Hellström-Lindahl et al., 2004). Although nicotine generally affects the facility of attention in a positive manner among healthy individuals, this effect is more pronounced in older people. And, in regard to long-term memory, it has no positive effect on consolidation. In another double blind study among patients with Alzheimer's disease, it was shown that the rate of error during cognitive tasks, the rate and suitability components of attention, and reaction time were all significantly elevated among people who received nicotine patch treatment, as compared to those given placebos (White and Levin, 1999). However, another study showed that after 4 weeks of nicotine patch treatment, no alleviation of memory dysfunction was seen, except improvement in short term memory (Snead et al., 1996). Nicotine antagonizes the harmful side effects of some anticholinergic drugs, such as scopolamine, which disrupt fast information processing tasks, and demonstrates a neuroprotective effect in experimental models of Alzheimer's disease, in both human and animal studies (Hellström-Lindahl et al., 2004; Janson et al., 1989; Jones et al., 1992; Newhouse et al. 2004). Although the mechanism by which nicotine improves both memory and attention performance in Alzheimer disease is not completely understood, it seems as though it

may be involved with nicotinic stimulation of the remaining cholinergic receptors and certain output pathways, such as the locus ceruleus noradrenergic and mesolimbic dopaminergic projections. Therefore, there is currently a great deal of research investigating the agonists of nAChRs in Alzheimer's disease treatment (Hellström-Lindahl et al., 2004; Mihailescu and Drucker-Colin, 2000; Newhouse et al. 2004).

CONCLUSION

When all of these concepts and hypotheses are taken into consideration, it seems that cigarette smoking among individuals who have schizophrenia may be a form of self-medication, and that the nicotine intake might help to mitigate the neuronal failure underlying this disease. In short, patients may unknowingly be trying to balance the biochemical and physiological dysfunctions in their bodies. Despite the many well-known health risks posed by the use of cigarettes, it is incredibly difficult for schizophrenic smokers to stop smoking cigarettes (Dolan et al., 2004). Many researchers have agreed that one of the most important reasons underlying this persistence of smoking might be the general positive neuropsychological effects of nicotine ingestion, strengthening the argument that it represent self-medication. This information might help to reduce cigarette smoking in schizophrenic people and it may also aid in finding new treatment options for schizophrenia.

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