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Review

Nicotine use in schizophrenia: The self medication hypotheses

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Abstract

The behavioural and cognitive effects of nicotine in schizophrenia have received much interest in recent years. The rate of smoking in patients with schizophrenia is estimated to be two- to four-fold the rate seen in the general population. Furthermore such patients favour stronger cigarettes and may also extract more nicotine from their cigarettes than other smokers. The question has been raised whether the widespread smoking behaviour seen in this patient group is in fact a manifestation of a common underlying physiology, and that these patients smoke in an attempt to self-medicate. We present an overview of the explanations for elevated rates of smoking in schizophrenia, with particular emphasis on the theories relating this behaviour to sensory gating and cognitive deficits in this disorder that have been viewed as major support for the self-medication hypotheses.

Keywords: Nicotine; Cigarette smoking; Sensory Gating; Prepulse inhibition of the startle response; P50 gating; Eye movements; Cognition; Genes; Schizophrenia; Symptoms; Antipsychotics; Side effects

Contents

1. Introduction

Nicotine has a wide range of behavioural and cognitive effects (Gray et al., 1994). It is extremely addictive; but, while over two thousand different compounds have been

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recognised in cigarette smoke, nicotine is generally acknowledged as the addictive substance accountable for sustained smoking behaviour (Jaffe, 1985; Stolerman and Jarvis, 1995). Several studies (de Leon et al., 1995, 2002a; Diwan et al., 1988;Glassman, 1993; Hughes et al., 1986) have shown that the rate of smoking in patients with schizophrenia is two- to four-fold the rate seen in the general population (20–35%). These observations remain true across cultures and countries and when controlling for possible confounds, such as marital and socio-economic status, alcohol use, antipsychotic use, or institutionalism (de Leon et al., 1995, 2002a; Glassman, 1993; Lohr and Flynn, 1992). Recent data indicate that the smoking rate in schizophrenia is also somewhat higher compared to that seen in other psychiatric disorders, such as mood disorder (de Leon et al., 2002b) and bipolar disorder (Uck et al., 2004). In the latter condition, prevalence and severity of smoking is found to be associated with the severity of psychotic symptoms (Corvin et al., 2001). There is some evidence that smokers with schizophrenia may also have a higher daily cigarette consumption (Uck et al., 2004), favour stronger cigarettes (Olincy et al., 1997a) and extract more nicotine from their cigarettes (Olincy et al., 1997a; Strand and Nyback, 2005) than normal smokers.

The reasons for the widespread smoking behaviour seen in schizophrenia are not well understood but several possible mechanisms have been advanced. Most of these suggest that nicotine serves as a form of self-medication to reduce the side effects of antipsychotic medications, to enhance the therapeutic effect of antipsychotics and so alleviate negative symptoms, and/or to ameliorate a number of cognitive deficits associated with schizophrenia. In addition to such clinical aspects, cigarette smoking has also been linked with the familial vulnerability to schizophrenia.

After a brief description of the complex pharmacology of nicotine, we will review and examine the evidence for the premise that the excessive rate of smoking and increased nicotine intake noted in schizophrenic patients serves as a form of self medication, as well as upholding a possible role for nicotinic agonist treatments in schizophrenia.

2. Pharmacology of nicotine

Many different effects of nicotine have been reported and considerable variation exists in how individual smokers are affected by the drug. Not all individuals who have been exposed to nicotine become addicted, thus raising the possibility that individual responses to nicotine might be genetically determined. The heritability estimate for tobacco smoking is found to be 53% (Gilbert and Gilbert, 1995). Genetic factors are also believed to influence the age at which individuals start smoking, and the number of cigarettes smoked per day (Heath and Martin, 1993). The cognitive effects of nicotine may be similarly predetermined. For example, although stress relief appears a universal experience (Wills and Shiffman, 1985), attentional enhancement is not always reported (Heishman et al., 1994; Wesnes and Warburton, 1983) and might only be experienced by individuals with a particular genetic makeup. This implies that there might be a subset of smokers who smoke for these attentional benefits, and others who smoke for other reasons. The possibility of (genetically driven) alternative motivating factors underlying the same drug use, in turn, might explain the variability observed in smoking behaviour.

The pharmacological actions of nicotine are complex, affecting a number of neurotransmitters (Gray et al., 1994). Nicotine is the major alkaloid of tobacco, first isolated by Posselt and Reiman from tobacco leaves in 1828 (Goodman and Gilman, 1980). The most common method of nicotine administration in humans is via inhalation of cigarette smoke. Following inhalation, nicotine is quickly absorbed into the systemic circulation via which it acts on almost every physiological system. The pharmacologically active form of nicotine closely resembles the acetylcholine (ACh) molecule, although nicotine is less flexible and only binds to one of the two types of cholinergic receptors, known as the nicotinic cholinergic receptors; this specific site of action was identified when comparing the effects of the neurotransmitter ACh with those of nicotine and the alkaloid muscarine, the latter of which acts on the muscarinic receptors.

2.1. Distribution of neural nicotinic receptors

Nicotine affects most bodily systems, however only the sites of action within the central nervous system are relevant to our current purposes. Nicotinic acetylcholine receptors (nAChRs), the main sites via which nicotine exerts its behavioural effects, are found in many areas of the brain and a number of studies have attempted to map their distribution. Animal studies using autoradiographic methods have located highest nicotine uptake in the hypothalamus, hippocampus, thalamus, midbrain, brainstem and areas of cerebral cortex (Clarke, 1993). Imaging studies of human subjects, using positron emission tomography (PET), have found the highest level of nicotine binding sites in the frontal, cingulate and insular lobes, as well as in the thalamus and basal ganglia (Nyback et al., 1989). Nicotine has been found to increase blood flow in the cerebellum and frontal lobes (Nagata et al., 1995). With functional magnetic resonance imaging (fMRI), nicotine has been found to produce the greatest increase in brain activity in the cingulate and frontal lobe regions including the dorsolateral, orbital and mediofrontal areas as well as in the areas which have been consistently put forward as mediating the rewarding effects of nicotine, namely the nucleus accumbens, amygdala and limbic thalamus (Stein et al., 1998).

2.2. Nicotinic receptor subunits

nAChRs are part of a superfamily of the ligand-gated ion channel class of neurotransmitter receptors, which also include glycine, serotonin 3 (5-HT3) and γ-aminobutyric acid (GABA). nAChRs consist of 5 subunits which cluster together to form an ion channel which opens once the related ligand binds to the appropriate site. Two varieties of neuronal nicotinic receptor subunits have been identified, namely α and β; each of which has a number of subtypes, each encoded by a separate gene (α2–α9 and β2–β4; Clarke, 1993).

Nicotinic receptors are distinguishable from each other by their own specific combination of subunits. These differently composed receptors are pharmacologically and functionally distinct as they present with different levels of affinity and sensitivity to various nicotinic agonists and antagonists (Patrick et al., 1993; Sargent, 1993). Autoradiographic binding studies in animals and humans have shown that there are at least three different types of neural nicotinic receptors, appearing at different sites in the brain.

The most common receptor (90% of nicotinic receptors) binds labeled agonists such as ^{3}H-nicotine with high affinity, while not binding α-bungarotoxin. Although there is some variability in the subunit composition of this receptor, it always features α4 and β2 subunits (McGehee and Role, 1995), appears in large quantities in the striatum and substantia nigra, and only in small quantities in the neocortex and hippocampus (Rubboli et al., 1994a,b; Sugaya et al., 1990).

The nicotinic receptor which has a high affinity for the snake toxin α-bungarotoxin is composed of five α7 subunits (McGehee and Role, 1995). It appears mostly in the midbrain, neocortex, thalamus and hippocampus, with lower levels in the striatum (Freedman et al., 1993; Rubboli et al., 1994a,b; Sugaya et al., 1990).

The third type binds neuronal bungarotoxin, contains α3 and β2 subunits (although, as with the most common α4β2 receptor, there is some variability amongst the other subunits) (Schulz et al., 1990), and is abundant in the hippocampus and in much smaller levels in the midbrain (Schulz et al., 1990; Sugaya et al., 1990).

The existence of so many different types of nicotinic receptor has consequences for the effects gained from smoking. As the multiple receptor subtypes also have different thresholds for nicotine, different doses of nicotine will achieve different pharmacological effects. The various subtypes of nicotinic receptor desensitise rapidly, that is they become insensitive to further (nicotinic) agonists following initial exposure, but they do so at different rates (Schoepfer et al., 1990). Thus, by titrating the amount of nicotine ingested, specific pharmacological effects can be gained as the control of dosage allows targeting of those areas that contain receptors most sensitive to (and least desensitised to) that particular concentration of nicotine. The most common method of administration of nicotine lends itself well to such titration, as inhalation of cigarette smoke results in almost immediate absorption of nicotine and thus the effects can be monitored by the user. Be it consciously or subconsciously, it may therefore be possible for a smoker to choose their dose to achieve the desired effect(s).

2.3. Nicotine–neurotransmitter interactions

Nicotinic receptors modulate the effects of a wide diversity of transmitter pathways, including the cholinergic system itself (by both pre- and post-synaptic mechanisms), and the dopamine (DA), glutamate, GABA, 5-HT, norepinephrine, opioid, and histaminergic systems (Gray et al., 1994; Levin and Simon, 1998). Of these, most is known about the modulation of dopamine and glutamatergic system with nicotine.

Animal studies have shown nicotine to differentially affect the two main dopaminergic pathways to the forebrain. Of these, the mesocorticolimbic system, which is thought to subserve limbic functions, begins in the ventral tegmental area, from which it projects to the nucleus accumbens, cortex, hippocampus, bed nucleus of the stria terminalis and amygdala. The nigrostriatal system, believed to subserve motor functions, begins in the substantia nigra and projects to the dorsal striatum, the caudate nucleus and putamen. The pleasureable and reinforcing effects of nicotine are believed to arise via an interaction of the drug with the mesocorticolimbic system. As is the case with other addictive drugs such as cocaine, these effects are believed to occur via an increase of dopamine levels in the nucleus accumbens (Corrigall et al., 1992; Henningfield et al., 1985; Imperato et al., 1986; Pich et al., 1997; Wise and Rompre, 1989) although a physiological interaction between nicotine and the cannabinoid system has also been implicated (Castane et al., 2002; Cohen et al., 2002, 2005). Some of the evidence suggesting that the reinforcing effects of nicotine arise via its interaction with the mesocorticolimbic system comes from studies where reduced self-administration has been observed following lesions to this pathway, or by infusion of nicotinic antagonists into the ventral tegmental area (Corrigall et al., 1994). The nigrostriatal pathway is not affected the same way by nicotine, as evidenced from different rates of dopamine release and metabolism in response to the drug. Studies using acute doses of nicotine in the rat have shown increased dopamine release and breakdown in the nucleus accumbens, but not in the dorsal striatum (Clarke et al., 1988). Equally, chronic exposure to nicotine results in decreased breakdown of dopamine in the dorsal striatum, while not having that effect in the nucleus accumbens (Kirch et al., 1987).

As mentioned before, it is likely that regional differences in proportions and combinations of nicotinic receptor subtypes might explain such region-specific patterns of nicotinic activation (Dalack et al., 1998). Such receptor differences might not only determine differences of nicotine

response between brain areas within an individual, but might also account for the different responses seen between individuals. Given the number of different receptor subunits, potential for unique combinations, each having their own particular pharmacological properties, is extensive. It is therefore possible that differences in combinations of receptor subunits also exist between populations, which might determine characteristic behaviour. Already evidence has been put forward for a differential expression of one such subtype of nicotinic receptor in schizophrenia (Freedman et al., 1997).

Nicotine also has a facilitating effect on glutamate transmission, although the mechanisms involved are less well documented than the drug's interaction with dopamine. It is thought that nicotine exerts this effect by increasing the speed of glutamatergic synaptic transmission in the cortex (Gray et al., 1996; Vidal and Changeux, 1993). This is most likely regulated by the α-bungarotoxin receptor subtype, as studies investigating this particular effect of nicotine in the hippocampus have shown that it can be blocked by administering α-bungarotoxin (Gray et al., 1996).

An effect not directly linked to nicotine, but relevant within the present context, is that cigarette smoking can decrease levels of many antipsychotics used to treat schizophrenia by as much as 50% by increasing metabolism and leads to requiring a higher dosage in smokers with schizophrenia to achieve therapeutic blood levels relative to non-smoking schizophrenia patients (Goff et al., 1992; Salokangas et al., 1997; Ziedonis et al., 1997). The suggestion has been made (Ziedonis et al., 1997) that this effect of smoking is most likely due to polycyclic hydrocarbons in cigarette smoke which stimulate the hepatic microsomal system, inducing liver enzymes to increase the metabolism of psychotropic medications.

3. Mechanisms mediating schizophrenia-cigarette smoking associations

3.1. Reduction in psychiatric symptoms

A percentage of patients report, in addition to the 'classic' reasons for smoking reported by healthy smokers, that smoking helps to reduce psychiatric symptoms (Glynn and Sussman, 1990), which some claim become worse during withdrawal (Dalack and Meador-Woodruff, 1996; Glynn and Sussman, 1990). There are few empirical clinical data directly testing these claims, but in one empirical study (Smith et al., 2002) smoking high-nicotine cigarettes, compared to smoking de-nicotinized cigarettes, was found to reduce negative symptoms without affecting positive symptoms. Such data primarily describe a therapeutic role of nicotine for *negative* symptoms of the disorder (i.e. avolition, apathy).

This effect is thought to reflect nicotine's ability to raise dopamine levels in the nucleus accumbens and prefrontal cortex (Corrigall and Coen, 1991). Following from the tenet that hypodopaminergic tone in the frontal cortex (i.e. hypofrontality) might give rise to these symptoms (Weinberger and Berman, 1988), it has been suggested that by raising dopamine levels in these regions, smoking provides a way of temporarily reducing these negative symptoms (Dalack et al., 1998). An increase in mesolimbic dopaminergic activity might help to activate psychomotor processes, such as active coping, improved attention and environmental engagement, and emotional responding, that commonly are absent in schizophrenic patients with prominent negative-symptoms.

Atypical antipsychotics, such as clozapine, which have shown the potential to decrease negative symptoms, are thought to do so by increasing cortical dopamine levels, possibly in a similar way to nicotine (Chouinard and Arnott, 1993). Clozapine is the most effective antipsychotic drug available so far and, like nicotine, it also has a complex pharmacology; it shows significant affinities for DA-D_1, DA-D_2, alpha$_1$, alpha$_2$, 5-HT_{2A}, 5-HT_{2C}, muscarinic and histaminergic receptors (Arnt and Skarsfeldt, 1998). There are data to show that clozapine also blocks 5HT-$_3$ receptors, resulting in release of acetylcholine, which would increase activity at nicotinic receptors and release of dopamine (Arnt and Skarsfeldt, 1998).

Interestingly, patients switching from typical to atypical drugs such as clozapine reduce their *ad lib* smoking levels (McEvoy et al., 1995a). It is, however, difficult to tease out the causes of these beneficial effects of nicotine on negative symptoms, such as anhedonia and social withdrawal. They could be explained by: increased activity in the reward system; nicotine's general effect of bringing about feelings of relaxation and well being; or be specific to the symptoms of schizophrenia per se. After all, the rate of smoking in this population far exceeds that seen in any other general or psychiatric population, including depressive illness where the benefits of a reward-system stimulant are obvious.

There have been only a few empirical investigations of nicotine withdrawal effects on symptoms of schizophrenia. In one investigation (Dalack et al., 1999), symptoms were monitored in schizophrenic patients while wearing either placebo or active nicotine patches during a three-day withdrawal period. Patients showed the classic symptoms associated with acute nicotine withdrawal, but exacerbations of psychotic symptoms were not observed with placebo patches. In another investigation (Yang et al., 2002), no difference in the effect of wearing nicotine or placebo patches during withdrawal on psychotic symptoms was found. These data suggest that problems patients might have during the early stages of smoking/nicotine withdrawal are not related to increased psychotic symptoms and, if so, the attraction of nicotine to schizophrenic patients must include further benefits.

3.2. Reduction in antipsychotic-induced side effects

There is evidence that smoking may help reduce unpleasant side effects of neuroleptic medication, specifically the Parkinsonian symptoms (Goff et al., 1992). The administration of nicotine via patches has been shown to reduce neuroleptic-induced akathisia (Anfang and Pope, 1997; Yang et al., 2002). Typical antipsychotic drugs such as haloperidol have a strong dopamine blocking action, and it is thought that smoking is able to provide relief from the related side effects through its efficacy in stimulating dopamine release. Some reports, however, contest the relationship between smoking and neuroleptic induced symptoms. For example, there is a report of greater movement abnormalities in patients who smoke than those who do not (Nilsson et al., 1997). However, the effects associated with smoking may involve factors additional to nicotine.

In addition to *physical* side effects, claims have also been made for a restorative effect of nicotine on the adverse effects of neuroleptics on *cognitive* functioning. Nicotine administered via a patch has been found to restore some of the haloperidol-induced disruptions in aspects of cognitive functioning such as cognitive slowing, spatial memory impairments and reduced attentiveness in schizophrenia patients (Levin et al., 1996); comparable effects of nicotine have recently been demonstrated also in the rat (Rezvani and Levin, 2004).

The relationship between medication and smoking appears to be specific to the type of neuroleptic used (Combs and Advokat, 2000), with reports confirming reduced rates of ad lib smoking in patients treated with clozapine compared to those treated with typical antipsychotics (Procyshyn et al., 2001, 2002) and following a switch from typical antipsychotics to the atypical drug clozapine (George et al., 1995). Smoking is also found to increase following haloperidol (McEvoy et al., 1995b) and to decrease following clozapine treatment (McEvoy et al., 1995a) compared with baseline (medication free) smoking levels in two patient groups. More recently, a relationship between nicotine use and responsivity to clozapine has been demonstrated (McEvoy et al., 1999); patients who smoke seem more likely to gain therapeutic benefits from clozapine than non-smokers. The pharmacology of clozapine described earlier (Section 3.1) together with the data mentioned here can be taken to suggest that nicotine and clozapine share some mechanisms for their behavioural effects. Supporting this suggestion are some recent data showing that clozapine improves deficient inhibitory auditory processing (see further) in DBA/2 mice, via a nicotinic cholinergic mechanism (Simosky et al., 2003).

3.3. Improvement in illness-related sensory gating and cognitive deficits

Rate of smoking, compared to the rate seen in the general population, is not only higher in patients with schizophrenia but also found to be two-to-four fold higher in a variety of neuropsychiatric populations such as attention-deficit hyperactivity disorder and Alzheimer's disease (Sacco et al., 2004). The suggestion has been made that nicotine may be effective in remediating some cognitive deficits associated with these disorders (Sacco et al., 2004). The strongest evidence for a role for nicotine in schizophrenia comes from studies showing sensory gating improvement with smoking/nicotine in schizophrenia patients. The two experimental paradigms of particular interest in this context are prepulse inihibition (PPI) of the startle response and gating of the acoustically elicited P50 wave, both of which reliably show deficient performance in this patient group. In addition, nicotine seems to exert beneficial effects on two eye movement tasks that have received particular interest in schizophrenia research, namely the smooth pursuit eye movement (SPEM) and antisaccade tasks, and also on some other cognitive measures that reliably reveal deficient performance in this patient population.

3.3.1. Prepulse inhibition

The simple startle reflexive response displays several forms of plasticity, both in animals and human beings. One form of startle plasticity is known as prepulse inhibition (PPI) which refers to a reliable reduction in the amplitude of the response to a strong sensory stimulus, the pulse, if this is preceded by 30–500 msec by a weak stimulus, the prepulse (Graham, 1975). This weak prestimulus is thought to evoke inhibitory mechanisms which limit further stimulation until the processing of the prepulse has been accomplished. This results in disrupted processing, and reduced impact of the pulse, and hence the PPI effect. PPI thus serves the function of avoiding behavioural interference that might otherwise occur from the simultaneous processing of discrete stimuli. Deficits in the ability to avoid such interference are thought to lead to sensory over-stimulation and behavioural confusion, for example as seen in schizophrenia (Braff, 1993). The most commonly used paradigms to demonstrate PPI effects in a laboratory setting employ a strong noise-burst as the pulse and a weak noise as the prepulse. In humans, electromyography (EMG) of the orbicularis oculi muscle directly beneath the eye has most frequently been used to index the eye blink response. In animal studies, PPI is usually measured as reduction in the whole body startle (jump) response to a prepulse-*plus*-pulse trial compared to the response to a pulse-alone trial (Swerdlow et al., 1994). A recent study using the eye blink startle response to assess PPI has, however, confirmed PPI in pigs (Arnfred et al., 2004).

Patients with schizophrenia reliably show reduced PPI (Braff et al., 2001) which seems to be more strongly associated with cognitive abnormalities and thought disorder than with schizophrenic symptoms (Perry and Braff, 1994; Perry et al., 1999). The neural substrates of PPI involve regions, mainly the hippocampus, amygdala, thalamus and basal ganglia (Kumari et al., 2003; Swerdlow

et al., 2001a), all of which are also implicated in the neuroanotomy of nicotine. There is also evidence of significant heritability in PPI in healthy subjects, with genetic factors contributing to over 50% variance of PPI (Anokhin et al., 2003). Animal studies too provide support for a genetic basis of mammalian PPI (Geyer et al., 2002), especially in showing genetically mediated strain-related differences in PPI and its modulation by pharmacological challenges (Swerdlow et al., 2001b, 2002), high heritability of PPI in mice (Bullock et al., 1997; Paylor and Crawley, 1997; Weiss et al., 2000) as well as mediation of PPI by certain quantitative trait loci in mice (Joober et al., 2002; Palmer et al., 2003).

Animal studies demonstrate that nicotine enhances PPI (Acri et al., 1991, 1994; Curzon et al., 1994) though in some studies this effect is found to be strain dependent (Faraday et al., 1999). More recently, nicotine has been found to attenuate the disruption of PPI with phencyclidine (PCP) in DBA/2J and C3H/HeJ but not in C57BL/6J mice (Spielewoy and Markou, 2004). PCP is a non-competitive antagonist of glutamatergic N-methyl-D-aspartate (NMDA) receptors; it also inhibits 5HT and DA reuptake, affects GABA function (Gerhardt et al., 1987; Smith et al., 1977) and blocks nAChRs (Pereira et al., 2002). The administration of PCP induces both positive and negative symptoms of schizophrenia in healthy subjects and exacerbates such symptoms in schizophrenia patients (Javitt and Zukin, 1991; Jentsch and Roth, 1999). Other data show that decreased prepulse inhibition during nicotine withdrawal in DBA/2J mice can be reversed by nicotine self-administration (Semenova et al., 2003). The effect of nicotine in some, but not all, strains suggests genetic influences in nicotine-induced modulation of PPI (which itself, as mentioned earlier, is under genetic control).

In humans, nicotine administered via cigarette smoking increases PPI in healthy smokers (Della Casa et al., 1998; Duncan et al., 2001; Kumari et al., 1996); a similar effect of nicotine administered subcutaneously is seen in non-smokers (Kumari et al., 1997a). More recent reports confirm that nicotine intake has a positive, though most likely transient, effect on PPI in people with schizophrenia (George et al., 2003; Kumari et al., 2001). The studies of nicotine influences in PPI in experimental animals, healthy human subjects and patients with schizophrenia, taken together, suggest that the excessive rate of smoking seen in schizophrenia may reflect an attempt to transiently remedy otherwise deficient PPI; this effect, however, may vary depending on genetic make-up.

While the accounts described in the previous sections have focussed on how nicotine may induce positive effects on negative symptoms and side effects of neuroleptic medication via its interaction with the dopaminergic system, such an explanation is unlikely to account for the improvement in PPI, as dopamine agonists have been shown consistently to disrupt PPI (Swerdlow and Geyer, 1998). Instead, the modulatory effect of nicotine in this measure may involve an interaction between the low affinity (i.e. α7 subunit containing) nicotinic receptors and glutamatergic transmission (Spielewoy and Markou, 2004). Selectively bred mice with low numbers of these receptors show reduced PPI, which is increased following nicotine administration (Bullock et al., 1997; Stevens and Wear, 1997). Some indirect support for this hypothesis includes findings of Kumari and colleagues (Kumari et al., 1997a) who reported that only a high dose of subcutaneous nicotine (12 μ/kg body weight) achieved increased PPI in healthy non-smokers, implicating low affinity nicotinic receptor involvement.

3.3.2. P50 gating

P50 refers to an evoked potential wave, which is elicited approximately 50 s following exposure to an auditory stimulus. P50 suppression refers to the reduction in P50 amplitude to a second, identical ('test') stimulus, when that stimulus is presented between 75–2000 msec after presentation of the first ('conditioning') stimulus. This inhibitory response is interpreted as reflecting a sensory gating mechanism (Adler et al., 1982). The P50 response, in contrast with the muscle response measured in PPI, is measured via electroencephalography (EEG). Thus P50, unlike the (PPI) startle paradigm, does not involve a motor response, the distinction between paradigms therefore is one of providing measures of sensory gating and sensorimotor gating respectively.

P50 gating has been found to be abnormal in patients with schizophrenia (Adler et al., 1982; Freedman et al., 1983). A role for nicotine in the improvement of sensory gating deficits in schizophrenia is further buttressed by observations of normalization of P50 gating deficits by nicotine in people with schizophrenia (Adler et al., 1992, 1993; Griffith et al., 1998) and their first degree relatives (Adler et al., 1992, 1993). Both schizophrenia and P50 gating deficit have been linked to the α7-nicotinic cholinergic receptor subunit gene locus (Freedman et al., 1997, 2001). These receptors are considered critical to this inhibitory response and post-mortem studies have revealed evidence of their abnormal expression and regulation (as well as that of other types of nicotinic receptors) in brains of schizophrenia patients (Breese et al., 1997, 2000; Freedman et al., 1997). Furthermore, agonists at this particular nicotinic receptor (GTS 21; DMXB-A) increase sensory gating in the rat and mouse (Stevens et al., 1998).

The modulatory effect of nicotine on P50 gating has been postulated to result from the nicotine-induced increases in glutamate release following activation of the α7 subunit containing nicotinic receptors. Leonard and colleagues (1996) suggest that gating of sensory input may depend on this interaction; increased glutamate release would facilitate release of GABA from interneurons, resulting in inhibition of the hippocampal CA3 and CA4 pyramidal neurons, the net result being suppression of the subsequent

response to the next stimulus. On the basis of such findings the Freedman group have proposed that a reduction or abnormality of α-bungarotoxin receptor subtypes in an individual would result in a decrease of cholinergic activation of inhibitory interneurons which would then result in reduced inhibition (Leonard et al., 1998; Martin et al., 2004). This deficient sensory processing might be improved by an increase in cholinergic stimulation of these particular receptors.

3.3.3. Smooth pursuit and anti-saccadic eye movements

Oculomotor dysfunction has been of interest in schizophrenia research since the beginning of the 20th century (Diefendorf and Dodge, 1908). The two eye movement tasks that have received most attention and consistently differentiated schizophrenia patients from healthy individuals are the smooth pursuit (SPEM) and antisaccade tasks. Smooth pursuit is typically measured in the human laboratory by presenting a stationary subject with a small visual target, such as a dot on a computer screen or a light emitting diode (LED), moving slowly in the horizontal plane and requesting the subject to follow the target with their eyes while keeping their head still. The key performance measure is pursuit accuracy. The antisaccade paradigm requires the subject to inhibit a reflexive saccade towards the target and instead initiate a saccadic eye movement in the direction opposite to the target. It examines the conflict between a prepotent stimulus that produces a powerful urge to saccade to the target, and the overriding goal to look in the opposite direction.

Studies have reliably shown that schizophrenia patients show impaired SPEM and generate a high percentage of errors on the antisaccade task compared to healthy individuals (Ettinger and Kumari, 2003). There is evidence for improved SPEM after acute administration of nicotine. Olincy and colleagues (1998) demonstrated that cigarette smoking improved SPEM performance which was otherwise deficient in smoker schizophrenic patients, but failed to show an effect in smoker non-schizophrenic controls. Another study from the same group later observed that SPEM gain improved in both smoker patients and controls after smoking, while small anticipatory, or 'leading', saccades improved only in the patient group (Olincy et al., 2003). Klein and Andresen (1991) reported a reduction in saccadic frequency during pursuit after smoking in both schizophrenia patients and healthy controls. Improved pursuit gain has also been observed after administration of nicotine using patches in smoker patients and controls (Dépatie et al., 2002) and nasal spray in patients (but not in controls) (Sherr et al., 2002). That the effects on SPEM seen with cigarette smoking extend to other means of nicotine delivery in patients, is important. It buttresses the idea that improvements are due to nicotine rather than some other non-specific factors associated with cigarette smoking.

Only recently, studies have begun to examine nicotine effects in anti-saccade performance in schizophrenia. The effects observed in one earlier mentioned study (Dépatie et al., 2002) suggest lower antisaccade error rates after administration of a nicotine patch relative to placebo in both schizophrenia patients and healthy controls. There are other findings which support these data. For example, the antisaccade error rate has been shown to be increased by overnight withdrawal from smoking in normal smokers and subsequently reduced by smoking before assessment (Powell et al., 2002). Another study (Roos et al., 1995) noted only slight improvements on error rate and latency after smoking one cigarette but they employed a short withdrawal interval and excluded subjects with more than a 50% error rate. This exclusion criterion can be considered problematic, as subjects in their study with the highest error rates improved most with nicotine. This last observation also has implications for the effects of nicotine on anti-saccade error rate in schizophrenia patients since they, on average, make more errors than healthy controls (Ettinger and Kumari, 2003).

The evidence available so far clearly points to beneficial effects of nicotine on SPEM and antisaccade deficits in schizophrenia patients, perhaps more so than in the healthy population. Given the complex pharmacology of nicotine, the current literature does not allow us to propose a definite mechanism for its effects on eye movement functions. One aspect of smooth pursuit tracking, leading saccades, has been linked to the same α7-nicotinic receptor subunit locus as the P50 deficit (Olincy et al., 1997b) so there might be some overlap in mechanism of nicotine effect on these two paradigms in schizophrenia. The errors on the antisaccade task (a measure of voluntary inhibition), however, are uncorrelated with degree of deficits on PPI of the acoustic startle (a measure of automatic inhibition as described previously) in schizophrenia (Kumari et al., 2005). This suggests that effects of nicotine in schizophrenia at the automatic and controlled processing levels may occur via different (perhaps over-lapping to some extent) neural circuits found to be deficient in schizophrenia. In some studies, anti-saccade error rate in schizophrenia patients is found to correlate with severity of negative symptoms (Ettinger et al., 2004a). Improvement in negative symptoms with atypical antipsychotic is considered to be associated with improved dopamine tone in the frontal cortex (Arnt and Skarsfeldt, 1998). The improvement in anti-saccade error rate with nicotine thus might also have a dopaminergic basis.

3.3.4. Attention, working memory and other functions

Brain areas found to be rich in nicotinic receptors have all been implicated in working memory, attention and motivation (Sawaguchi and Goldman-Rakic, 1994), which in turn are all reported to be susceptible to the modulating effects of nicotine (Warburton, 1990). Studies in experimental animals as well as in human beings have shown that nicotine/nicotine ligands exert a wide range of behavioural effects, including improvements in a variety of cognitive

functions, while nicotine antagonists, such as mecamylamine, impair these functions (Levin and Rezvani, 2002; Levin and Simon, 1998). The cognitive effects of nicotine/nicotine ligands in experimental animals have most reliably been revealed in terms of improved attention and working memory performance and occur after both acute and chronic treatments (Levin and Rezvani, 2002; Levin and Simon, 1998). Selective nicotinic agonists, such as dimethylaminoethanol (Levin et al., 1995), epibatidine (Levin et al., 1996), isonicotone, norisonicotine (Levin et al., 1999), (E)-metanicotine (RJR-2403) (Lippiello et al., 1996), or lobeline (Terry et al., 1996) have also been shown to improve performance.

Nicotine, administered via cigarette smoking, skin patches or subcutaneous injection, has been shown to improve attention/information processing and working memory measures in smoking-deprived healthy human smoking populations (Foulds et al., 1996; Heishman et al., 1994) as well as in non-smoking populations (Le Houezec et al., 1994). While it could be argued that nicotine-induced cognitive improvements in smoking-deprived subjects reflect restoration of performance deficits caused by nicotine deprivation (Hatsukami et al., 1989), performance enhancement with nicotine in non-smoking subjects with no pre-existing deficits as well as in experimental animals suggests a true beneficial effect of nicotine. Nicotine is known to increase cortical arousal, as measured with electroencephalographic techniques (Knott et al., 1999), which in humans is thought to be closely associated with the quality of attentional efficiency and thus a potential mediator of enhanced cognitive performance (Eysenck, 1982). More recently, fMRI studies, specifically focussing on the neural correlates of cognitive effects of nicotine in healthy humans, have confirmed the involvement of brain regions, such as anterior cingulate and thalamus, which are known to be implicated in attention and arousal in nicotine-induced cognitive improvements (Kumari et al., 2003; Lawrence et al., 2002).

Schizophrenia is associated with multi-faceted cognitive deficits, including impairments in learning, memory, attention, executive functioning, and cognitive processing speed (Sharma and Antonova, 2003), some of which appear to transiently improve with nicotine. Nicotine is found to improve sustained attention (Lohr and Flynn, 1992) and reverse abstinence-induced deficits in spatial working memory in schizophrenia patients (George et al., 2002). Nicotine nasal spray is reported to improve spatial accuracy and verbal memory (Smith et al., 2002). Nicotine patch has been reported to improve performance on an attention task (Continuous Performance test) in one study (Dépatie et al., 2002) although nicotine nasal spray failed to affect performance on this task in another study (Sherr et al., 2002). More recently, nicotine administered via patches to smoking deprived schizophrenia patients was reported to improve their performance on a task involving working memory and attention and increase activation and functional connectivity of brain regions including anterior cingulate and thalamus (Jacobsen et al., 2004); this effect was not seen in healthy smokers again suggesting that patient with schizophrenia might be gaining more attentional benefits than other smokers. Another recent study of schizophrenia patients (Harris et al., 2004), however, failed to detect positive effects of nicotine on tests of immediate or delayed memory, language or visuo-spatial attention; it showed evidence of improved attention with nicotine in non-smokers but not in smokers. Furthermore, in one of the previously described studies (George et al., 2002), quitting smoking for up to 10 weeks was reported to worsen spatial working memory, but to have no effect on performance of schizophrenia patients on the Stroop test, a measure considered to tap executive functioning and selective attention.

An effect of being a smoker on some functions has also been described in the literature. For example, Silver and colleagues (2002) reported a relationship between smoking status and finger tapping rate, as a measure of central processing, in schizophrenia patients treated with atypical antipsychotics. Smoker patients showed significantly faster finger tapping rates than non-smoker patients and this was not related to clinical state, illness chronicity, medication side-effects, antipsychotic dose or plasma concentrations. Smoking is also considered to normalize olfactory identification in schizophrenia patients which otherwise is found to be deficient in this population (McLean et al., 2004).

Overall, existing evidence points consistently towards the beneficial effect of smoking/nicotine on sustained attention and working memory functions in schizophrenia, perhaps to a greater extent than seen in healthy populations. Other cognitive functions may be less sensitive to the effects of nicotine/smoking.

3.4. Familial vulnerability to schizophrenia

Smoking seems not only to be associated with clinical aspects and cognitive deficits of schizophrenia, but also with being a relative of a schizophrenia patient. Unaffected co-twins of schizophrenia patients are found to show significantly higher rates of daily smoking and reduced success in attempts to quit than controls (Lyons et al., 2002). These observations perhaps are not surprising since there is evidence for a substantial genetic contribution to the predisposition to schizophrenia (Gottesman, 1991) and a proportion of relatives of schizophrenia patients also show cognitive and attentional impairments that are seen in patients themselves (Braff and Freedman, 2002).

There is evidence for reduced PPI (Cadenhead et al., 2000) and reduced P50 gating in relatives of schizophrenia patients (Waldo et al., 1991, 1995). Similarly, a number of studies have demonstrated impaired SPEM in about 50–80% of schizophrenia patients and 30–40% of their first-degree relatives, compared to about 8% of healthy

individuals (Ettinger et al., 2004b; Lencer et al., 2003; Levy et al., 1993). SPEM impairments show concordance in monozygotic twins discordant for schizophrenia (Holzman et al., 1980). There is considerable evidence also for genetic transmission of antisaccade abnormality in schizophrenia from family and twin studies (Ettinger and Kumari, 2003). Further abnormalities in relatives of schizophrenia patients include deficient sustained attention (Chen et al., 1998; Erlenmeyer-Kimling, 2000), and structural (Faraone et al., 2003) and functional brain deficits (Callicott et al., 2003) all of which may be relevant to the influence of nicotine. There are no published data, to our knowledge, examining the influence of nicotine on PPI or eye movements in relatives of schizophrenia patients, but there is reliable evidence of transient improvement with nicotine/cigarette smoking in P50 gating (Adler et al., 1992, 1993).

In addition to the relatives of schizophrenia patients, healthy individuals with high levels of schizotypy, who are considered to be phenotypically related to people with schizophrenia, have been reported to smoke at increased frequency compared to the general population (Williams et al., 1996). As is the case with relatives of schizophrenia patients, such individuals also display schizophrenia-relevant deficits such as reduced PPI (Cadenhead et al., 2000), disturbed latent inhibition (Baruch et al., 1988) and eye movement abnormalities (Ettinger et al., 2005; Gooding et al., 2000; O'Driscoll et al., 1998; Siever et al., 1994). There is preliminary evidence that cigarette smoking might normalize some of these deficits such as reduced PPI (Kumari et al., 1997b) and latent inhibition (Williams et al., 1996) in individuals scoring high on schizotypy measures who otherwise would show deficient performance. These observations pertaining to effects of nicotine in populations genotypically and/or phenotypically related to schizophrenia further buttress the suggestion that self-administration of nicotine via cigarette smoking serves a form of self-medication to correct for sensory and cognitive deficits in schizophrenia.

High prevalence of cigarette smoking has been reported even before the clinical manifestation of schizophrenia in affected individuals (Weiser et al., 2004). A very recent birth cohort study (Riala et al., 2005) links cigarette smoking to the prodromal phase of schizophrenia. These observations might suggest that impaired nicotinic neurotransmission is involved in the pathophysiology of schizophrenia and that perhaps such individuals suffer from schizophrenia related cognitive deficits even prior to clinical manifestation of the illness and smoke in order to gain a temporary relief.

4. Possible reasons for nicotine-intake/heavier smoking in schizophrenia

We mentioned in the first section that, aside from the high prevalence of smoking in people with schizophrenia, such smokers may absorb more nicotine from the cigarettes than do other heavy smokers (Olincy et al., 1997a; Strand and Nyback, 2005; but see Bozikas et al., 2005). Such a titration strategy would appear consistent with a targeting of low affinity nicotinic receptors.

However one of the big challenges facing those attempting to explain the mechanisms via which nicotine might produce favourable effects in schizophrenia is that of rapid desensitisation of nicotinic receptors, which incidentally may also account for the transient nature of the improvements to sensory gating reported above. Desensitisation is not problematic if large numbers of receptors are present and available for activation, as only proportions of these will become desensitised at any one time (Freedman et al., 1995).

Chronic smokers show an increase or upregulation of nicotinic receptors, an effect thought to compensate for the otherwise total desensitisation following nicotine use. This increase directly reflects the amount of cigarettes smoked, and is reversible after cessation of smoking (Breese et al., 1997). A comparison of such binding sites in the hippocampus, cortex, thalamus and caudate reveals that, unlike healthy smokers, patients with schizophrenia do not show the normal upregulation of nicotinic receptors following chronic nicotine use (Breese et al., 1997).

5. Conclusions

To conclude, there is considerable empirical support for the idea that smoking in schizophrenia may represent an attempt to self-medicate some of the cognitive deficits of this disorder. Proposed are a wide range of beneficial effects of nicotine which are explained in terms of the drugs' interaction with dopaminergic as well as glutamatergic transmitter systems. Given that cigarette smoking lends itself to titration to achieve specific pharmacological effects, it is possible that individual patients may use different dosing strategies to achieve such effects. Combined, such observations stress the importance of pursuing the development of nicotinic agonist treatments (Levin and Rezvani, 2002; Martin et al., 2004). Over the last decade attempts have been made to develop $\alpha 7$ selective agonists such as DMXBA, 3-(2,4-dimethoxybenzylidene)-anabaseine (Kem, 2000). Such developments appear promising but are yet to be formally tested for their efficacy in treating impaired sensory gating, cognitive dysfunctions and negative symptoms of schizophrenia (Martin et al., 2004). Future studies exploring the effect of similar substances in schizophrenia could potentially prove to be influential in advancing the development of nicotinic agonist treatments for this disorder. Treatments specifically targeting dysfunctions in nicotinic–glutamatergic interactions and capable of effectively treating cognitive deficits in schizophrenia would be particularly useful. Potentially such a treatment strategy would not only be a useful advance in treatment of

schizophrenia but also, by providing an alternative to smoking, reduce the harmful effects, such as elevated risk for cardiovascular disease (Goff et al., 2005), due to chronic smoking in this population.

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