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Review Article

The Symptomatic Importance of Nicotine in Schizophrenia

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Abstract

The tendency of people suffering from schizophrenia to consume more cigarettes and thus put themselves at a much greater risk of cardiovascular and respiratory disease is well-known. This is an obvious health consideration for people who are already more vulnerable to ill-health because of a mental illness which is notoriously difficult to manage. There is a wealth of information available detailing the importance of nicotine in the pathophysiology of schizophrenia: some important examples from this body of work will be reviewed here. Chronic Nicotine Replacement Therapy (NRT) such as with 12- or 16-hour transdermal nicotine patches are not appropriate for achieving the necessary improvements in cognitive function in schizophrenia. A better alternative is NRT which replicates the short burst of nicotinergic activity that cigarette smoking provides. Nicotine chewing gum, or more controversially, e-cigarettes, are the two clear candidates. Nicotine inhalators have been largely unsuccessful as agents for the delivery of nicotine, as the sensation that they produce is a reportedly unpleasant one. The use of nicotine gum or e-cigarettes is not something which would necessarily break the habit. In people who suffer from schizophrenia and who are supplementing their deficient endogenous cerebral nicotine with exogenous sources, delivery via gum or e-cigarettes represents a far less toxic route than tobacco cigarettes. In the latter, it is probable that the aromatic hydrocarbons in cigarette smoke also cause the increased metabolism of antipsychotic drugs due to their induction of hepatic catabolic enzymes. This adds another negative factor to tobacco cigarette consumption for people with severe mental illnesses. For a patient group which is already at risk of impaired physical health, prevention of respiratory and cardiovascular pathology is especially important. The success of clozapine and olanzapine as antipsychotic medications is in large part due to their success in improving the deficient sensory gating inherent to schizophrenia. These drugs are also associated with greater success in helping schizophrenic smokers to abstain; both of these aspects can be at least partly attributed to their involvement of cerebral nicotinic receptors. Where it is not possible for the schizophrenic smoker to abstain, then as clinicians, we are duty-bound to research acceptable alternatives to smoking. It is also possible that NRT delivered via safer methods such as gum or e-cigarettes can provide a useful adjunct to antipsychotic treatment. For these reasons, the symptomatic role of intermittent NRT in schizophrenia must be further investigated.

Keywords: Schizophrenia; E-cigarettes; Nicotine Replacement Therapy

Sensory Gating in Schizophrenia

Of central importance to this area is the function of nicotine in the brain. Dalack et al. [1] sound the cautionary note that no single explanatory model can account for the inconsistent symptoms of the range of schizophrenic illnesses. In spite of this, I must admit to being impressed by the central importance of nicotine. This is largely due to the wide distribution of nicotinic cholinergic receptors in human neurophysiology and their consequent multiplicity of actions. It is often said that 'there is no blood test for schizophrenia'. However, the lack of e.g. P_{50} or P_{300} inhibition in the two-click paradigm (explanation follows) is a robust and universally replicated finding in both people with schizophrenia and their first degree relatives [2,3]. This then is effectively a 'blood test' for liability to schizophrenia. Additional hippocampal pathology is needed before the sensory gating liability revealed by the two-click paradigm leads to psychosis [4].

The two-click paradigm is where EEG recordings of cerebral activity are taken in response to two auditory stimuli, usually loud clicking noises against a background of white noise. The interval between the clicks is can be 300 milliseconds or 50 milliseconds – hence ' P_{300} 'or' P_{50} 'responses, referring to the observed cerebral response to a second auditory stimulus at respectively three hundred milliseconds or fifty milliseconds after the first auditory stimulus [2,5]. Usually, people show a burst of activity detectable on the electroencephalogram over the temporal areas after the first auditory stimulus. If a second stimulus is rapidly delivered, such as 50, 200 or 300 milliseconds later, the amplitudes of EEG recordings from the same areas are reduced. This is indicative of sensory gating, where attention is maintained upon the initial stimulus, such that neurological processing of it can be completed [2]. The fact that a second stimulus applied up to 500 milliseconds later produces a

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reduced cerebral response demonstrates that the bulk of directed sensory attention is still occupied by the first stimulus. It has been repeatedly found that people with schizophrenia and their first-degree relatives show a lack of inhibition of the second stimulus – this is referred to in the literature as a lack of, e.g., P_{300} inhibition, or a lack of pre-pulse inhibition or lack of PPI. The lack of PPI, demonstrates a tendency to impairment of sensory gating. Importantly, however, as noted by Adler et al in 1998 "*…additional hippocampal pathology may be critical for…psychosis to develop*" (my emphasis). So, while unaffected first-degree relatives of people with schizophrenia may have had a reduced PPI, they had also been found to have normal-sized hippocampi. This finding has consistently been replicated in the last thirty five years (e.g. Braff et al. [2]).

The hippocampus is operative in learning, particularly in visuospatial and auto-associative learning [5]. Sensory gating is imperative in optimal learning: when the learning process is functioning at its peak effectiveness, irrelevant stimuli are disregarded, such that attention can be focused on what is deemed important. For this process, efficient sensory gating is essential. Another important function of sensory gating is to screen out repetitive irrelevant stimuli. This process is therefore operative in habituating to repetitive stimuli. If, for example, the noise of a repeatedly creaky door or the rattle from an old radiator cannot be screened out, it should be understandable how such now-intrusive stimuli may acquire delusional significance. Delusions can be readily comprehended as a conscious attempt to make sense of pathological cerebral phenomena. If a person who is psychologically unwell begins to perceive repeated stimuli, these can readily acquire a delusional significance: it must be stated that the attribution of delusional significance only occurs where the necessary constellation of neurological symptoms is already present. So, hypothetically: 'every time that door creaks, the people hunting me down are coming nearer'. This is an example of delusional perception; if the cerebral dysfunction is long-standing, the explanatory delusions can become systematized.

Nicotine and Sensory Gating

The importance of hippocampal nicotinergic function in schizophrenia is in the maintenance of sensory gating [6]. At area CA 3 of the hippocampus, i.e. Cornis Ammonis area 3, about 10% of neurones are inhibitory GABAergic neurones. Hippocampal area CA3 is an important relay area, as it receives innervation from a wide range of cerebral areas. So, as well as receiving meso-limbic and prefrontal cortical dopaminergic input, neurons from the serotonergic midbrain raphe nuclei and the noradrenergic locus coerleus synapse here. This demonstrates how CA3 is potentially of central importance in the integration of afferent and efferent cerebral signalling. With particular regard to schizophrenia, the specific receptor of interest here is the nicotinic cholinergic α_7 receptor: this has been shown to be genetically linked to PPI [5]. The α_7 receptor is a ligand-gated ion channel: the ligand is nicotine and the ion is the bivalent calcium Ca2+ ion. Sufficient nicotine allows influx of calcium via the receptor and so, depolarization of inhibitory interneuron's in this area. Notably, the α_7 receptor is a low-affinity one, thus requiring high doses of nicotine to activate it. The receptor also desensitises quickly [1]. Because of this, administration of nicotine via 12 or 16-hour epidermal patches would desensitize the operant nicotinic receptor. These patches are therefore unsuitable as a mode of adjunctive treatment in schizophrenia. Acute nicotine administration, such as that obtained by smoking a cigarette, by chewing nicotine gum, or – currently controversially – by the use of an e-cigarette, transiently reverses the loss of PPI. Sufficient nicotine is needed to activate the cholinergic α_7 receptor because of its low affinity. People suffering from schizophrenia have reduced numbers of nicotinic receptors [7]: the epigenetic effect of smoking - to increase the level of circulating nicotine – was observed to normalize the deficient responsible gene operation in schizophrenic people. This was confirmed by work on post-mortem sampled cerebral tissue from people with schizophrenia who did and did not smoke [8]. The responsible gene (CHRNACh7) lies at 15q14 [4]. In their investigation of post-mortem schizophrenic cerebral tissues, Mexal et al. found that the expression of the nicotinic acetyl choline α_7 receptor (α_7NACHr) had been differentially expressed between smokers with schizophrenia and non-smokers with schizophrenia [8]. They also found that both groups also differed from control non-smokers in the expression of CHRNACh7.

E-cigarettes as Nicotine Delivery Agents

The controversy regarding e-cigarettes was alluded to in a very recent article in the British Medical Journal [9]. [The same article was subsequently published in the 'i' newspaper in the UK, 18.7.2015.] Here, the difference between the "pragmatists and idealists" was remarked upon. Practicing clinicians often took the role of pragmatists who, being conscious of the importance of harm reduction in people who do not wish to stop smoking, endorse the potential use of NRT possibilities such as e-cigarettes. The pragmatists are contrasted with the idealists, who tend to be public health specialists. The idealists are horrified by the tobacco companies' attempts to re-define themselves as agents who are promoting healthier alternatives (e-cigarettes) while continuing to produce tobacco cigarettes that contribute to the ill-health and death of millions of people worldwide annually. –

"…If the big tobacco companies were genuinely concerned about the disease and harm they caused…they would go into e-cigarette production 100%" (Quoted in Gornall et al. [9]).

…However, from a realistic point of view, the actions of multinational companies are never simple activities with a binary outcome of good or bad, quite apart from their economic objectives, which tend to have the casting vote in deciding future actions.

To leave the murky world of financial interests versus health-promoting interests, and return to the safer area of neuropharmacology (!) it is clear that the cerebral role of nicotine is an important one. It has a central role in sensory gating at inhibitory hippocampal interneurons, which is of fundamental importance in schizophrenia [1,4,5].

Nicotine in Cerebral Salience and Reward Circuitry

Another factor of symptomatic interest is the attribution of salience [10], and in cerebral reward circuitry [11,12]. Gradin et al. investigated reward processing in schizophrenia with fMRI (functional Magnetic Resonance Imaging) [10]. They found that the system which switches between the resting cerebral mode and an attention-directed salience circuit between the insula and anterior cingulate cortex

does not function correctly in schizophrenia. The relevance of this to nicotinergic function in schizophrenia is that nicotinic cholinergic receptors are operative in attribution of attention and attribution of reward. Significantly, antipsychotic medication wasn't found to be a confounder in this study. It isn't specified, unfortunately, whether the patients were taking clozapine or olanzapine. These two medications have significant nicotinergic activity which quite probably contributes to their efficacy. Where salience is abnormally attributed, as with the example given regarding sensory gating earlier, it should be easily understandable how conscious psychotic explanations could be generated, where sufficient related pathology is also present, to render these phenomena intelligible to the affected person. The involvement of nicotine in cerebral reward circuitry is exemplified by the fact that nicotine also reinforces behaviour by allowing dopamine release from the Nucleus Accumbens and Ventral Tegmental Area [11]. α_7 NACHr s are involved here: presynaptic α_7 NACHr enhance glutamatergic (=excitatory) transmission in other limbic nuclei. α_7 NACHr desensitize very rapidly; the glutamatergic mechanism is longer-lasting and solidifies the reinforcing effects of nicotine. The activity of nicotine alters synaptic function in the ventral tegmental area, contributing both here and in other cerebral areas to the establishment of learning and memory. The hedonic element of learning, i.e. the feeling of subjective reward when something is learned, is mediated by dopaminergic discharge in the meso-limbic system [1]. This is influenced further neurologically upstream by the activity of NACHr [12]. Closer investigation of the pharmacology of the NACHr has demonstrated that those receptors which include the β_2 subunit are involved in addiction [13]. As a result of this discovery, together with the long-standing knowledge of the importance of NACHr, agonists at the latter are under investigation as therapeutic agents in schizophrenia [14]. By concentrating solely on α_7 NAChR, it is hoped that the therapeutic gains of nicotinergic agonism can be achieved without the potential addictive problems which have been attributed to the β_2 NAChR [13].

Integration of Research on Cerebral Nicotinergic Activity

A very recent article in Lancet Psychiatry [15] diverges from the existing work regarding smoking and mental illness. Although these authors reviewed 3717 studies, they did not include any examples from the sizeable body of work on nicotine and schizophrenia. Gurillo et al. [15] note that "…tobacco use is associated with increased risk of psychosis and an earlier age of onset of psychotic illness." (ibid.) Exactly the same association was noted by McEvoy and Brown in 1999 [16]: these authors are members of one of the many international research teams to have closely investigated the link between smoking and psychosis. They, like others, have found nicotine to be the operative factor. Instead of attributing a hitherto unknown ability of smoking to cause mental illness (as seems to have been suggested by Gurillo et al. [15]), McEvoy and Brown [16], building on pre-existing work in this area, suggested that smoking might exert independent therapeutic effects, separately from antipsychotic medication, and is a marker for more severe types of schizophrenia. Their conclusions of course draw on the accumulated work on nicotine and schizophrenia, which had been amassing since at least 1986 (e.g. Hughes and Hatsukami [17]). One of the authors, McCabe, has implied that smoking tobacco cigarettes might represent a causal factor for psychotic illness and that 'causality might work in either direction'. As mentioned above, none of the studies which they reviewed included any examples of the work on nicotine and schizophrenia. Of course, it must also be remembered that association does not always imply causality. The reasons which underlie any association must be carefully explored, as has been the case for smoking and schizophrenia: the operative factor in the association was found to be nicotine. It is now evident that nicotine is important in sensory gating, in the attribution of salience and in reward processing. All of these are of clear importance in the pathogenesis of psychotic mental illnesses, particularly schizophrenia.

The ultimate question is how can these findings be translated into patient benefit? With regard to smoking and schizophrenia, there is clear evidence for the smoking as self-medication theory with regard to disrupted sensory gating and schizophrenia. The influence of direct nicotinic activity in reward circuitry and the attribution of experience is evidence of the variety of neurophysiological effects of this substance. The fact that agonists at the α_7NACHr are being investigated as potential pharmacological therapeutic agents for schizophrenia presently is one example of a potential therapeutic use of the accumulated knowledge. Examples of these drugs include Encenicline, ABT-126 and AQW051 [18]. The latter is specifically being developed to treat disruptions in cognitive function resulting from schizophrenic illness. It will be very interesting to see whether this new drug is effective in people with chronic schizophrenia, and thus the long-standing neurological damage associated with this illness.

Another route might be to try and use this knowledge in a more direct way: the use of exogenous nicotine delivered in a safer form than tobacco cigarettes. It may be that exogenous nicotine from chewing gum or e-cigarettes could act as a useful adjunctive treatment for schizophrenia. Certainly, one important issue regarding e-cigarettes is that the liquid additive components used in them are unregulated [19]. Because of this, there are safety concerns regarding the use of e-cigarettes. In spite of this, they are far safer agents of nicotine delivery than tobacco cigarettes. This certainly seems to be a worthwhile topic to investigate. The prize is improved cardiovascular and respiratory health in a vulnerable group of people, and a better understanding of the therapeutic potential – or otherwise – of NRT such as e-cigarettes.

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