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Short Article

Nicotine and Cerebral Neurotransmission

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Nicotine is a co-factor in cerebral neurotransmission: one of its functions is the maintenance of the tonic level of hippocampal sensory gating. Its importance in this role is best exemplified by the excessively high rate of cigarette smoking in people who suffer from schizophrenia. Such people tend to consume more cigarettes, and attempt to extract the maximum nicotine dose from them [1]. (Kumari and Postma 2005). The advent of e-cigarettes is something that should be greeted with interest by the medical communities – especially by psychiatrists. In the case of schizophrenia, the drive to smoke is very probably an attempt at self-medication, to replenish deficient central nicotine reserves. The cerebral significance of nicotine is that it allows the inhibitory action of the hippocampus to function at an optimal level [2,3]. In schizophrenia, nicotine has a particular role is in the maintenance of the correct level of sensory gating [3-7]. This not only reduces positive symptoms of schizophrenia, but is most probably operative in reducing negative symptoms caused by excitotoxicity [8].

Cholinergic (nicotinic) hypofunction has been detailed as part of the pathological process in schizophrenia [9] hence ingestion of exogenous nicotinic agonists might ameliorate this [1,10]. If the chosen method of ingestion is via cigarette smoking – as is usually the case – then people who suffer with schizophrenia are also ingesting carcinogens and other toxins. The benefits of ingesting nicotine by a method other than cigarette smoking should be evident. The seminal study by Doll and Bradford Hill in 1954 demonstrated that lung cancer is directly attributable to cigarette smoking. The carcinogenic factors in cigarettes include tar, carbon monoxide and aryl hydrocarbons (i.e. those hydrocarbons containing an aromatic ring). Inhalation of these substances is carcinogenic, as well as being directly hazardous to respiratory health. Passive inhalation is similarly dangerous to active inhalation – and this is probably the reason why smoking has now been banned in UK NHS premises.

The provision of nicotine replacement therapy (NRT) for people who are attempting to give up smoking is deemed sage enough to be available from high street pharmacies. NRT in this context is available as adhesive skin patches, chewing gum, lozenges, nasal spray and inhalers. The very recent introduction of e-cigarettes is an intriguing development in this regard. Of course, e-cigarettes were not intended to be part of the panoply of NRT. Their current lack of standardisation and regulation make them especially problematic in this respect, but as recently said in the British Medical Journal "It is probably a lot better to be a vaper [an inhaler of e-cigarettes] than a tobacco smoker...I'd much rather put relatively pure nicotine into my lungs as the mix of ingredients found in burned tobacco" [11]. It is surely not beyond the ability of food and drug legislators to design an assessment and rating system of e-cigarette delivery systems.

Cigarette smoking is very probably a mode of self-medication in schizophrenia to treat deficient cerebral nicotinic transmission [1,5,10]. The important nicotinic function here is differentiation of neuronal impulses from varying sources. The alpha 7 nicotinic cholinergic receptors (NAChR 7) in hippocampal area CA3 are operative in working memory and hence increased sensory gating and inhibitory mechanisms [3,6]. Therefore, agonism at NAChR 7 leads to a higher rate of inhibitory neuronal firing.

Positive symptoms in schizophrenia are related to overactivity in the mesolimbic system: deficient sensory gating contributes to this clinical phenomenon. When sensory gating functions correctly, one is able to screen out background stimuli, such as the noise of traffic outside a window. If the person is unable to do this, as in acute schizophrenia, the now intrusive stimulus may acquire a delusional significance [3]. Sensory gating also appears to allow an individual to differentiate between internally-generated and extrinsic experiences. Therefore adequate nicotinic activation at hippocampal area CA3 is

hypothesised to reduce positive schizophrenic symptoms [7].

With particular regard to sensory gating in schizophrenia, the α7 nicotinic receptor desensitises quickly [9]. Therefore, in attempting to replace deficient cerebral nicotine, intermittent exogenous sources are probably better than continuous nicotine patches. This is where the e-cigarette system is of interest, as the short-acting enhancement of cerebral nicotinic transmission could potentially be useful. As well as the prevention of acute positive symptoms of schizophrenia, the prevention of excitotoxic cerebral damage is equally important [8,12]. Unremitting stimulation of a cerebral neurone leads to exhaustion of its contents and subsequent cell death by apoptosis [2,13]. This is exactly analogous to status epilepticus, one reason why the latter is so dangerous. Every acute attack of schizophrenia further destroys cerebral neurones via excitotoxicity (*ibid.*) resulting in negative symptoms. The pathology of schizophrenia is so aggressive that negative symptoms can be seen in a first attack of the illness. Nicotinic receptor stimulation allows the correct level of hippocampal inhibition – via sensory gating – to occur. Therefore, stimulation of nicotinic receptors is potentially useful in addressing negative symptoms of schizophrenia – or importantly, in preventing them. It is worthwhile to consider a trial of e-cigarettes with a clear nicotine dosing regimen as a treatment adjunct in schizophrenia. It is quite possible that this form of nicotine administration may provide a useful adjunctive treatment for schizophrenia. A criticism that has been made of e-cigarettes is that their faithful reproduction of the oral and manual activity of tobacco cigarette smoking may lead to the former being a gateway to the latter. However, it is equally possible that 'vaping' [using e-cigarettes] may become a socially acceptable pursuit in its own right. This is particularly the case with younger users, who would see vaping as an exclusive phenomenon and possibly not participated in by older people. Indeed, one advertising tagline for an e-cigarette system declares that 'smoking is so last season'.

To reiterate, the advent of the e-cigarette system represents an opportunity to investigate the utility of this as a type of NRT which has utility in those not willing to stop – such as people with schizophrenia. The contraindications to NRT generally are unstable cardiovascular disease: it remains a clear theoretical possibility that vaping would preclude the respiratory and vascular damage caused by cigarette smoking, thus potentially removing one of its contraindications. This is an opportunity to improve the care of schizophrenia that should not be ignored.

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