THE IMPACT OF NICOTINE AND SOCIAL DRINKING BEHAVIOUR AND BRAIN FUNCTION

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Abstract

Nicotine acts on nearly every Physiological System of the human body. The effects of nicotine on the Peripheral nervous system have been extensively studied and are now quite well understood. The effects of nicotine on the central nervous system are more complex and our understanding of these effects is limited. The Pharmacokinetic and Pharmacodynamics of nicotine with an emphasis on the Psychopharmacological basis of nicotine dependence. In South America, seeking for psychoactive effects of nicotine might be as old as the origin of horticulture, beginning some eight thousand years ago present Ritual tobacco was used in shamanism aimed to achieve acute nicotine intoxication, which induced in the shamans' catatonic states representing symbolic death. The effect of large doses of nicotine on the autonomic and central nervous system gave the impression of a gradual death of the shaman, who then returned miraculously to life (Wilbert 1987). Regular, moderate use of nicotine alone or in combination is a well-known, widely established and loved practice of men and women both. Despite, health consequences to these pharmacological agents, people continue, quite persistently, to consume these substances and afford much value to the pleasure of a regular intake.

Keywords: Addiction, Psychoactive substances, Respiratory, Nicotine

Introduction

The assumption is that, in general nicotine has stimulating effects, while alcohol has sedating effects, surprisingly, in situation of both positive and negative excitement, as wedding, the birth of child, or in challenging of stressful situation or in boredom or monotony, people may choose the pleasure of either a cup of strong coffee, the smell of a cigarette or the refreshment of a beer or glass of good wine. As moderate and regular non-smokers users of coffee and alcohol there are several motives. There is relatively little information on the effect of the combined use of these substances which is astonishing in views of the regular use

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and enjoyment of these substances in varying combination. Relatively little is known about the effect on brain function associated with sensation, perception attention and memory, although there is a great effort going on in different research centers to get a more precise picture of these effects, on information processing as assessed from brain activity.

Nicotine the major alkaloids of tobacco was first isolated in a pure form by Posset and Reimann in 1928. Nicotine and other alkaloids (atropine, muscarine curare alkaloids) have played a key role in the development of knowledge, and understanding of the functional organization of the autonomic nervous system. At the turn of the 19th century, Langley and his colleagues used nicotine to determine the nature of the autonomic innervation and the location of ganglionic synapses for many organs. The concept of receptor arouse from Langley's experiments. The concept of specific receptors that bind drugs or transmitter substances onto the cell, thereby either initiating biological effects or inhibiting cellular functions, is today a cornerstone of pharmacological research and pharmaceutical development. Yet, while the basic ideas of this concept were first explicitly formulated in 1905 by the Cambridge physiologist John Newport Langley (1852–1925). In 1914, Dale developed the concept of two different sites of action of acetylcholine termed muscarinic and nicotine (Le Houezec and Benowitz 1991).

Tobacco smoking is a unique and highly addictive form of systematic drug administration in that entry form of systematic drug administration, in that entry into the circulation is through the pulmonary rather than the portal or systematic venous circulations. Nicotine reaches the brain in less than 10 seconds, faster than after intravenous administration. Thalamus, midbrain, brain stem and in areas of the cerebral cortex.

Nicotine also binds to Nigro striatal and mesolimbic dopaminergic neurons. Brain nicotine concentration increases sharply after completion of smoking, then declines over 20 to 30 minutes as nicotine redistributes to other tissues (Benowitz et.al 1990).

This results in transient high brain concentration of nicotine, which acts on many neurotransmitters and produces reinforcing blood concentration decline more slowly, reflecting blood concentration from body tissues and the rate of elimination (half-life over aging 2 hrs.) In contrast to inhalation, other routes of

absorption result in gradual increase in nicotine concentration in the brain, and a low brain-to-blood ratio. These routes are considered as less addictive form of administration.

Pharmacokinetic and Pharmacodynamics of Nicotine

The reinforcing properties of a drug are expected to be stronger when positive, subjective effects quickly follow self-administration. If the effect of the drug is delayed due to slower absorption or if tolerance to the drug develops quickly. The abuse liability of this drug is slow. Slow delivery system present consequently, a low abuse potential (Henning field and Keenan 1993) whereas abuse potential of nicotine nasal spray and aerosol is probably higher because their kinetic profiles are close to that of smoking. However, the distribution of kinetic of nicotine, venous blood levels may not reflect levels at the site of action. To examine the importance of distribution kinetics in the apparent development of acute tolerance to nicotine, (porchet.et.al. 1987) compared effect of rapid and slow loading infusions of nicotine, followed by maintenance infusion venous blood nicotine levels, similar in both condition did not explain the much greater cardiovascular and subjective effects of nicotine during the rapid compared to the slow-infusion concentration of nicotine in the brain were simulated using a model incorporating distribution kinetics in arterial blood and the brain derived from studies in Rabbits (Benowitz et.al.1990), while Pharmacodynamics analysis of nicotine effects based on venous levels which underestimate brain level, incorrectly indicated acute tolerance, simulated brain concentration showed no tolerance. In other words, nicotine brain levels more closely resembled the heart rate acceleration curve than did venous blood levels. It was observed, however, that a late peak (30 minutes) in venous nicotine concentration was not accompanied by a peak in heart rate.

This cannot be explained by distributional tolerance, but rather indicates true tolerance. To characterize the time course of tolerance development and regression, a study in which subjects received paired intravenous infusion of nicotine, separated by different time intervals was conducted (porchet.et.al.1988). Despite higher blood concentration, heart rate and subjective effects were of much less magnitude after the second compared to the first infusion when separated by 60 or 120 minutes, when 210 minutes separated the two infusions, the response was fully restored. The Pharmacokinetic - Pharmacodynamics model developed from

the study indicated a half-life of development and regression of tolerance of 35 minutes thus after 1.5 to 2 hours (3-4 half-lives) of steady-state exposure to nicotine, tolerance is almost fully developed. This model also suggests that tolerance is not total and that 20 to 25 percent of the expected pharmacological effect at a similar level of nicotine in the non-tolerant state persists. These Pharmacodynamics studies suggest that nicotine effects in a smoker will persist during the daily smoking cycle despite the development of some acute tolerance. The intervals between 2 cigarettes may be influenced in part by the fluctuation of tolerance during this cycle.

The first cigarette of the day produces substantial pharmacological effect, but at the same tolerance begins to build. The duration of time until the next cigarette is smoked may be determined as the time at which there is some regression of tolerance but before severe withdrawal symptoms appear with succession of cigarettes, there is accumulation of nicotine in the body resulting in greater level of tolerance. Transiently, high brain level of nicotine after each individual cigarette may partially overcome tolerance, but the reinforcing effects tend to lesson throughout the day. In accordance with the elimination half-life of two hours, nicotine is almost totally eliminated from the body after overnight abstinence, allowing desensitization to actions of nicotine (Benowitz, 1990). Full desensitization, however, may require days (lee et.al.1987). Chronic tolerance to nicotine in human subjects, need to be studied more systematically. This will require to compare regular smokers to nonsmokers (chippers) as well as to nonsmokers.

Psychopharmacological Effects of Nicotine as Reinforcers of Tobacco Dependence

Nicotine has numerous effects on physiological systems, but its action on the central nervous system is of particular interest in that such actions presumably reinforce smoking behavior. There is evidence that smokers can adjust their nicotine intake to optimize mental functioning and to control their mood (Le Houezec et.al. 1996). There is no doubt that a drug that facilitates shifts towards optimal cognitive Performance and positive affect may stimulate rewards system as does any other seeking behavior (Ashton and Golding 1989). (Le Houezec and Benowitz, 1991) People who are likely to use these reinforcing properties of

nicotine are probably at greater risk for dependence and for severe withdrawal symptoms during smoking cessation. The research from our laboratory is based on the hypothesis that the improvement of mood and cognitive function by nicotine is a powerful reinforcer of tobacco dependence.

Cognitive Performance

Many studies have found that cigarette smoking or nicotine administration improves mental health functioning in abstinent smokers (U.S department of Health and Humans Services, 1988). It is likely that improvements in cognitive Performance could be a major factor in why people smoke and could explain why they find it difficult to quit smoking (Le Houezec and Benowitz, 1991).

Interest in nicotine effect on human performance has been growing as can attest special issue on nicotine published in Psychopharmacology (vol 108, No 4 September, 1992). However, this body of research has serious methodological limitation (Le Houezec and Benowitz, 1991). The performance observed after smoking is due to relief of symptoms of abstinence or to primary effect of nicotine on the brain, or even a combination of both (Hughes, 1991). A study by Snyder and Colleagues (1989), illustrating the effect of relief of the symptoms of abstinence assessed the decrement of performance of smokers during a 10 days period of abstinence, using a battery of cognitive test. Impairment of performance was observed within 4 hours after the start of the deprivation period, peaked between 24 and 48 hours. And then returned towards baseline values, however, some performance deficit remained throughout the 10 days of abstinence. Resumption of smoking at the end of this period resulted in return of performance to baseline when within 24 hours. In contrast, a study by West and Hack (1991) illustrated the direct effect of nicotine by showing an improvement of short-term memory using Stemberg's memory. Search task (Kole. et. al, ch-9, Zeef. et. al. ch-16) subjects were presented for 3 seconds with a list of 2 or 5 digits, termed the memory set. The author tested occasional and regular smokers before and after a nicotine or a nicotine free cigarette and before and after 24 hours of abstinence, the memory search rate was significantly increased in both groups after nicotine cigarette compared with the nicotine free cigarette, but only for the larger memory set. These results suggest that nicotine act specifically on memory scanning, an effect never reported before with any other drug. Interestingly, there was no difference in

result between the occasional and regular smokers and no influence of abstinence. The role of nicotine itself in determining the effect of smoking on performance, in most of the studies is generally inferred but rarely been directly assessed. Neither actual nicotine intake nor nicotine blood levels have been measured or controlled.

Most studies have experimentally manipulated the type of cigarettes comparing cigarette with low and high nicotine delivery or the number of cigarettes smoked. Neither of these measures account for inter-individual variability in smoking behavior and Nicotine absorption (Borowitz and Jacob, 1984). (Feyerabendian et.al, 1985) The improvement observed after nicotine is due to changes in specific mental processes (e.g. attention) or reflects a more general effect on all mental processes (e.g. arousal effect). The use of reaction time RT the time between the presentation of a stimulus and the subject's response is not sufficient to answer analysis of Event Related Potential ERP components, extracted from the electroencephalogram, gives indexes of information processing stages and allows one to distinguish between the perceptive and the motor segment of information processing, and to approach the chronometry of mental functioning (Dunchin 1979). (Renault et.al. 1988) The appearance of the P 300 wave (a positive wave occurring 300 to 600 MS after a stimulus presentation) is considered to reflect the end of the stimulus processing, a remainder of the RT representing the response processing. Thus, increasing response complexity will only both increase P 300 latency and RT, while increasing response complexity will only affect RT with no effect on P300 latency another component. The N100 wave (a negative wave occurring around 100ms after a stimulus presentation) reflects the physical characteristics of the stimulus as well as some aspects of attention (Luck et.al., 1990).

Affective Effect of Nicotine

There is some evidence that smokers may be able to control their mood as well as their cognitive function (Carton et.al. 1994), (Le Houezec et.al.1995, 1996) there is also some evidence that a history of major depression, even in remission is associated with greater difficulty in smoking cessation (Anda et.al 1990). (Glassman et.al.1999) occurrence of mood perturbation as a smoking withdrawal symptoms may then represent a negative prognostic for smoking cessations.

People who are likely to 'use' these reinforcing properties of nicotine may present specific personality dimensions like arousal seeking which may predispose them to dependence, one of our hypothesis links energetic deficit encountered in some psychiatric diseases (depression, schizophrenia, degenerative, pathologies) to frontal hypo activity implicating dopaminergic pathways. Due to its direct action on dopaminergic system (Balfour. 1994) nicotine could be considered as a self-medication of such deficits. This hypothesis is the result obtained in one subject recruited as an anhedonia person (loss of pleasure) who pretended to use smoking as a psychostimulant drug. This subject was not depressed at the time of the test but had a history of recurrent major depression major episode. He came twice in the morning after overnight abstinence from smoking. We recorded his ERP in a classical oddball task before and 2 hours after either smoking of 3 small cigars or taking of a single dose of dopaminergic antidepressants drug. ERP traces in both conditions appeared to be very similar.

In comparison with each of the pre - drug (abstinence) conditions, a similar shift to the ERP traces towards the lift (Speeding of information processing) was observed in both post drug conditions. This result which needs to be replicated suggests that nicotine may produce a cortical activation through the stimulation of dopaminergic pathways. If it is confirmed this could be evidence of a behavioral trait.

(Stimulating smoking with anti-anhedonia effect) which may expose this type of smokers to a greater risk of development of a depressive episode during smoking cessation. The next step is our study in smokers trying to quit smoking with nicotine replacement therapy (transdermal systems) Evaluation of cognitive function ERP and mood changes (clinical evaluation) are made before and during the treatment.

Dose Response Effects

Nicotine is known to have a complex dose response relationship. Langley's early week on nicotine, at the turn of the century, have shown that low doses of nicotine stimulate ganglion cells while high doses produce a short stimulation followed by a blocking effect. This biphasic response is observed in vivo as well although the mechanism is far more complex. Smoking has been reported to have both stimulating and calming effects. However, if it is clear that nicotine effects may be

interpreted in terms of increased activation of autonomic and central nervous system. The evidence that high doses of nicotine obtained from smoking have opposite effects is far less convincing. The relaxing effect of nicotine could be conditioned response secondary to the Peripheral muscles relaxing effect of nicotine induced by inhibition of the Renshaw cells of the anterior horns of the spinal cord. Moreover, comparison of the effect of acute nicotine with the effect of chronic tobacco use should be made with caution. Before extrapolating pharmacological observation from animal to humans, blood concentration should be measured to ensure that the effects are being studied in a portion of the dose response curve relevant to smokers.

Conclusion

Several issues still need to be addressed in order to better understand both the actions of nicotine on the central nervous system and their implication in tobacco dependence. One of these issues concerns the tolerance to nicotine effect on information processing. Most of the studies that have been conducted, including, the one in non-smokers, but give no information concerning chronic nicotine use. There is a need for studies in different populations (non-smokers, ex-smokers, regular and occasional smokers) to better understand the role of tolerance. Moreover, as we observed huge difference in nicotine may greatly differ among individuals. In this view at might be necessary to better characterize the personality and mood of subject as well as their pharmacological response to nicotine.

Action of nicotine on the central nervous system is of particular interest in understanding why people smoke. The complexity of the relationships between nicotine and the neurotransmitters leaves considerable gaps in the understanding of dependence. The current knowledge on nicotine receptors is fragmentary. The same is true for mechanisms of tolerance, which probably play an important role in nicotine dependence. Many studies have reported improvement of cognitive function. However, most of the results are inconclusive performance by acting directly on the brain or namely by relieving the symptoms of abstinence it is also unclear whether nicotine improves task performance by affecting specific mental processes or whether it has a more global effect on all mental processes. The research from our laboratory is based on the hypothesis that the improvement of mood and cognitive function by nicotine is a powerful reinforcer dependence. The

result of this study would help to better understand the role of affective and cognitive perturbation in failure of smoking cessation attempts.

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