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Nicotine dependence: development, mechanisms, individual differences and links to possible neurophysiological correlates

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Nikotinabhängigkeit: Entwicklung, Mechanismen, individuelle Unterschiede und Beziehungen zu möglichen neurophysiologischen Korrelaten

Zusammenfassung. Neue Erkenntnisse zeigen, dass die Mehrzahl der Tabakkonsumenten raucht, um die psychopharmakologischen Eigenschaften des Nikotins zu erleben, welches im Tabakrauch enthalten ist, und ein signifikanter Anteil der Tabakkonsumenten abhängig von der Substanz Nikotin wird. In den USA wurden 80% der Raucher, in Europa 39% der Raucher nach den diagnostischen Richtlinien der American Psychiatric Association als abhängig klassifiziert. Als Resultat wird Nikotin selbst, in diesem Fall auch Nikotinersatz genannt, von einer steigenden Zahl von Rauchern als Entwöhnungshilfe verwendet. Das Ziel dieses Reportes ist es, in einer relativ einfachen Sichtweise, Mechanismen herauszuarbeiten, die bei der Entwicklung und Aufrechterhaltung der Nikotinabhängigkeit beteiligt sind.

Schlüsselwörter: Nikotin, Tabak, Rauchen, Abhängigkeit.

Summary. There is now little doubt that the majority of people who smoke tobacco do so to experience the psychopharmacological properties of the nicotine present in the smoke and that a significant proportion of habitual tobacco users become addicted to the drug nicotine. In the US some 80% and in Europe (Germany) 39% of smokers have been classified as dependent according to the diagnostic guidelines of the American Psychiatric Association. As a result, direct nicotine replacement is used increasingly by many people who want to stop smoking. The objectives of this review are to outline the mechanisms involved in the development and maintenance of nicotine dependence and to link behavioural observations to possible neurophysiologic correlates.

Key words: Nicotine, tobacco, smoking, drug dependency.

Introduction

There is now little doubt that the majority of people who smoke tobacco do so to experience the psychopharmacological properties of the drug nicotine present in the smoke and that a significant proportion of habitual tobacco users become addicted to nicotine. In the USA 80% [1] and in Europe (Germany) 39% [2] of smokers have been classified as dependent according to the diagnostic guidelines of the American Psychiatric Association [3]. As a result, direct nicotine replacement [4, 5] is used increasingly by many people who want to stop smoking. It is becoming clear, however, that nicotine and nicotine analogues also influence neural systems in the brain that are thought to be implicated in a range of psychiatric and neurological disorders, and that the putative therapeutic properties of these compounds therefore may extend beyond a treatment for tobacco dependence [6].

The objectives of this report are to outline the mechanisms involved in the development and maintenance of nicotine dependence and to link behavioural observations to possible neurophysiological correlates. Some of this will be speculation, but it is hoped that new hypotheses will guide our research and help further our understanding of the reasons for nicotine use.

The pathophysiology of tobacco dependence

The fundamental pharmacological effect of nicotine is its action on the nicotinic acetylcholinergic receptors (nAChRs) (Fig. 1). These receptors are located primarily in central nervous system (CNS) regions of cholinergic transmission. Although nicotine directly activates only the nicotinic and not the muscarinic receptors, the end result is often a complex pattern of indirect effects on other transmitter systems such as the dopaminergic and adrenergic systems. The effects of nicotine on the nAChRs in the autonomic system are probably less involved in the subjective pleasurable effects and production of dependence than the effects mediated by the nAChRs in the brain. Activation of central nAChRs may result in beneficial effects of nicotine such as cognitive enhancement and increased control over arousal and negative emotions [7]. An exception to the primary role of brain nAChR beneficial effects may be the metabolic and lipolytic processes involved in weight control, which seem to be more peripherally mediated [8].

Neuroadaptation

Like acetylcholine, nicotine stimulates the nAChRs, but nicotine seems to keep the receptors depolarised for

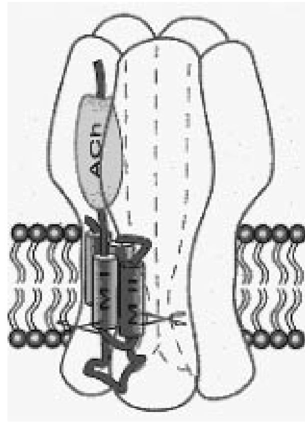

Fig. 1. Neuronal nicotinic receptor. This receptor gene family is likely to be involved in release of multiple neuro-transmitters in both brain and peri-phery that mediate sensitivity and tolerance to nicotine. Leonard S, Bertrand D (2001) Nicotine Tob Res 3: 203–223

longer than acetylcholine. Nicotine therefore has a dual effect: stimulation of the receptor–agonist function, followed by a receptor blockade–antagonist function. Both these effects interfere with normal functioning in nicotine intolerance, therefore the nervous system, and particularly the CNS, needs to adapt to the disrupting effects of nicotine. Blocking appears to be a more significant effect than stimulation because the brain adjusts and overcomes blocking, rather than stimulation, by upregulating the number of nicotine receptors [9]. Neuroadaptation can be seen as the organism's means of defence against the toxic effects of nicotine. Besides these qualitative changes, there are also quantitative changes. It has been found that new very-high-affinity subtypes of nicotinic receptors can develop on polymorphonuclear blood cells [10]. To what extent these findings from leucocytes reflect the nicotinic receptors on neuronal tissues is not fully known.

A schematic and highly hypothetical illustration of nAChR status as a function of the degree of addiction or neuroadaptation is shown in Figs. 2a–d. Under normal conditions, a certain number of nAChRs are available for acetylcholine transmission (Fig. 2a). After exposure to tobacco smoke and initial stimulation, some of these receptors are blocked, leaving the cholinergic system partially blocked (Fig. 2b). With continued smoking this blockade serves as a stimulus for upregulation to compensate for the antagonistic effect of nicotine (Fig. 2c). The upregulation is dependent on the mode of administration. Chronic infusion of nicotine has been associated with greater upregulation than injections [11], and it is thought that those who smoke more often and with shorter intervals are administering nicotine in a way that is more conducive to receptor upregulation, compared with those smoking just a few cigarettes per day with long intervals between. If nicotine administration is finally stopped, the system will have too many nAChRs, which may result in hypercholinergic activity and withdrawal symptoms (Fig. 2d). The objective for the cholinergic nervous system when nicotine administration stops is to readapt to a nicotine-free state: this readaptation will take different times for different individuals. It is not known how long readaptation takes, nor is it known how long it takes to upregulate nAChRs. In rats and mice the initial neuroadaptation has been found to vary with, for example, the nicotine dose, route of administration and brain site [11]. Upregulation, usually with an increase in receptor density of ~50%, can occur from days to several weeks [11, 12]. In mice, readaptation seems to occur much faster than the original upregulation [13].

Tolerance

The neuropharmacological correlates for tolerance may have to do in part with the process of neuroadaptation. Possibly the number of receptors or degree of upregulation is related to *long-term tolerance*, whereas *acute tolerance* may be linked to the actual state of the receptor: that is, whether it is in a sensitised or desensitised state.

The underlying process of neuroadaptation and dependence may be illustrated by the development of smoking in a naïve smoker such as an adolescent. When smoking the very first cigarette, a few puffs will cause mild

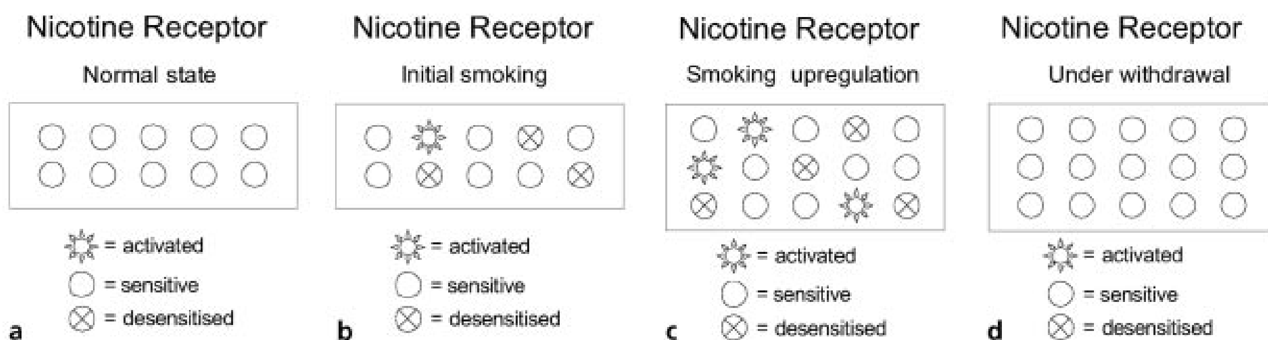

Fig. 2 a–d. The status of the nicotinic acetylcholinergic receptors as a function of the degree of addiction or neuroadaptation. Under normal conditions, a certain number of nAChRs are available for acetylcholine transmission (**a**). After exposure to tobacco smoke and initial stimulation, some of these receptors are blocked, leaving the cholinergic system partially blocked (**b**). With continued smoking this blockade serves as a stimulus for upregulation to compensate for the antagonistic effect of nicotine (**c**). If nicotine administration is stopped, the system will have too many nAChRs, which may result in hypercholinergic activity and withdrawal symptoms (**d**)

intoxication, whereas 10–20 years later the same person can inhale the smoke from 40–50 cigarettes per day with tolerance. The dose of nicotine delivered from 40–50 cigarettes per day for an intolerant subject could be very serious and possibly fatal. For a dependent smoker the problem comes when nicotine is not administered. Then the system first signals craving – compulsion to use – followed by various withdrawal symptoms, often resulting in relapse for a smoker who may have the strongest intentions to give up. It is in this situation that pharmacological treatments such as nicotine replacement [14, 15] may be needed, to provide some of the nicotine the dependent individual needs to function properly. After some time the nicotine dose can be decreased slowly with an accompanying readaptation in the nAChRs. The mechanism for bupropion treatment for tobacco dependence is largely unknown; however, it may to some degree 'cover' and protect the ex-smoker from the experience of withdrawal symptoms while allowing time for the readaptation of the nAChRs. Pharmacologically, bupropion is a weak inhibitor of the neuronal uptake of norepinephrine and dopamine and an antagonist of nAChRs. Its efficacy in smoking cessation may be through the effect of the dopaminergic activity on areas of the brain that are responsible for the reinforcement properties of addictive drugs, together with the effect of noradrenergic activity on nicotine withdrawal [16]. Bupropion should be evaluated for its impact on the primary target population (smokers who are interested in quitting) [17].

The withdrawal symptoms (Table 1), of which the most important are craving, irritability and anger, difficulty in concentration, impatience, anxiety, dysphoria and weight gain [3], usually peak within 2–3 days. However some symptoms, like craving and weight gain, can last much longer. It seems that some long-term tolerance can last for a long time in some smokers. For example, someone may have been an ex-smoker for a number of years, then one day may smoke a cigarette, followed by another ten the same day. Without some residual tolerance, it is difficult to understand how so many cigarettes could be smoked in one day without intoxication. A study monitoring nAChRs on polymorphonuclear granulocytes – which may function differently from nAChRs in the CNS – found that it took a year for highly dependent smokers to downregulate the number of receptors. The smokers in that study also had very-high-affinity receptor sites, which are not observed in non-smokers [10]. This difference took approximately a year to disappear. There is thus evidence that upregulation and possibly tolerance to nicotine can be long lasting, and as long as there is remaining tolerance it is possible that this will translate into suboptimal day-to-day performance and functioning.

Table 1. Nicotine withdrawal symptoms

Dysphoria
Insomnia
Irritability, frustration and anger
Anxiety
Difficulties concentrating
Restlessness
Decreased heart rate
Weight gain
Impatience
Craving

An example of how acute tolerance or tachyphilaxis relates to the state of nAChRs may be seen in the morning smoking habit. After overnight abstinence, the smoker's nicotine concentrations in blood and brain tissue have normally dropped considerably because of the relatively short half-life of nicotine: approximately two hours. Thus, most receptors are in a sensitive state and are readily stimulated when the first nicotine binds to the receptors. Many smokers – and particularly heavy smokers because of their more profound upregulation – experience some light headiness or dizziness from the first cigarette in the morning. For most regular smokers, these effects are not experienced with any other cigarette during the day because short-term tolerance builds up as the receptors rapidly become desensitised.

The half-life of tolerance probably varies in different physiological measurements, but for cardiovascular effects it has been estimated to be approximately 35 minutes. This indicates that about two hours after smoking a cigarette – approximately four half-lives – near full sensitivity should have been regained for the cardiovascular system [18]. This relatively short half-life of tolerance to cardiovascular effects may be the reason for the fairly flat dose-response curve for cardiovascular disease and the amount of tobacco smoked [19]. However, the half-life of tolerance is only 3.5 minutes for increases in energy expenditure, and at the other extreme, no tolerance at all develops to the free fatty acid concentrations that reflect lipolysis [20].

Individual differences

So far we have described some general effects of nicotine that are thought to be of relevance for the majority of smokers. In the remainder of the paper we discuss biological factors that might influence the acquisition of the smoking habit and the development of dependence for individual smokers, such as nicotine tolerance, genetic influences and gender effects.

A 'social' smoker is usually less dependent on nicotine than the daily smoker who might have drug-induced changes in affect and performance. A small number of smokers are inconsistent users, smoking from one or two cigarettes a day up to four or five packs a day. Such smokers might even have their sleep interrupted by nicotine cravings [21]; however, most appear to smoke 10–30 cigarettes a day.

What makes some smokers more dependent than others?

Nicotine tolerance

It has been suggested that the initial sensitivity to the effects of nicotine when adolescents first experiment with tobacco could be a factor that influences the course of further smoking [22]. This theory postulates that those who are most sensitive, i.e. those having the strongest intoxica-

tion effects, will be more likely to develop dependence because of pressure towards neuroadaptation to neutralise these effects. In a study by Pomerleau et al., groups of smokers with high and low-dependency, ex-smokers and never smokers were questioned about their reactions to the first cigarettes of their life. It was found that pleasurable sensations, 'rush' and/or 'buzz', and relaxation were significantly more likely to have occurred *in those who later became smokers.* The ratio of pleasant to unpleasant sensations, computed as an index of overall hedonic impact of initial exposure, also favoured the likelihood of developing a habit. Unpleasant effects, nausea and cough did not differ significantly among the groups. People who became highly dependent cigarette smokers had more pleasurable sensations at their initial exposure to tobacco, and unpleasant reactions to the first cigarette did not seem to protect against subsequent smoking [23]. These results were replicated in a small study where questionnaires were given to a number of smokers (n = 32) asking them to rate the effects of their very first cigarette. When the smokers were categorised into high or low nicotine dependence using the Fagerström test for nicotine dependence [24], an insignificant trend towards greater sensitivity for negative effects was seen for the highly dependent smokers. These smokers reported significantly stronger positive effects compared with smokers with low dependence. However when nicotine was given subcutaneously to current and former smokers and to those who had never smoked, the results were inconclusive for the predictions of this theory [25]. A prospective study on alcohol uptake [26] found results that contradicted those of Pomerleau et al. [23], therefore findings on initial sensitivity as a determinant of dependence development must be taken as preliminary.

Data from experiments in animals suggest that concurrent release of adrenal cortex hormones might be related to sensitivity to nicotine [27], and differences have also been found in the gene for alpha-7 nicotine receptors [28]. Thus it is a paradox that those who initially experience intense adverse effects will become more dependent smokers than those who suffer less intense initial effects. These preliminary findings suggest that the positive effects experienced from initial smoking are a stronger determinant for development of dependence than the adverse effects, to which tolerance seems to develop rapidly.

Genetic influences

The heritability index for smoking has generally been found to be around 50% or about the same or higher than the genetic influence for alcoholism and coffee drinking [29]. Strong genetic influences have also been seen in the way in which mice and rats react to nicotine [30]. Studies on monozygotic and dizygotic twins have shown that heredity influences the uptake of a smoking habit, being a current smoker or ex-smoker and the amount smoked. The strongest contribution of heredity seems to be on the persistence of smoking: being more dependent and failing to quit [31]. A recently published meta-analysis indicates that genetic factors play a more significant role in smoking initiation (SI) than in smoking persistence (SP) in women compared with men. Significant gender differences were also detected in shared environmental factors for SI and SP; however, no significant gender difference was detected for unique environmental effects for either phenotype [32]. It has been found that Afro-Americans – but not Caucasians – with a defective gene responsible for dopamine synthesis were at higher risk of becoming smokers, having earlier onset with more difficulties in stopping and shorter latency to smoking the first cigarette after awakening in the morning [33]. The time to first cigarette of the day is generally regarded as the best single indicator of dependence [34].

Two personality dimensions that are thought to have a genetic component, namely novelty-seeking and extroversion, have been linked to initiation and persistence of smoking [35]. Much of the research on genetic influences is directed at genes involved in regulating the dopaminergic system. Lerman and Swan have recently updated this area of very disparate findings [34]. Although the findings are still equivocal, some studies have found an increased prevalence of the A1 and B1 alleles of the dopaminergic receptor gene DRD2 among smokers [36].

Smoking may also be influenced by the way in which nicotine is metabolised, as Europeans and East Asians may metabolise nicotine differently [33]. Nicotine is metabolised almost exclusively by the enzyme CYP2A6, the gene for which can have full activity ('wild type') or may be more or less defective. Smokers with defective CYP2A6 alleles metabolise nicotine more slowly and are less likely to become smokers and, if they do smoke, tend to smoke fewer cigarettes [37]. Nicotine dependence, as assessed by the Fagerström test for nicotine dependence [37], appears to correlate with the activity of the CYP2A6 system (Tyndale, Rachel, personal communication 1999).

Gender effects

In animals (rats and mice), males have higher densities of nicotine receptors, i.e. more upregulation [12], and experience more arousal and exploration than females. There also seems to be a stronger effect on anxiety and energy expenditure [38].

Among humans, women seem to be less discriminating in their nicotine intake than men [39] and regulate their nicotine concentrations less precisely [40]. Women smoke more than men in response to negative effects [41] and weight concerns [42], and the association between smoking and depression seem to be stronger for women [43]. Quitting seems to be somewhat more difficult for women [44] and often they compensate by making more frequent attempts. Desire to smoke to relieve negative effects increases in the late luteal phase when women have higher pre-menstrual symptomatology [45], thus it may be advisable to recommend women to avoid quitting in the late luteal phase and to try in the follicular phase. However, difficulties in stopping often last longer than a single menstrual cycle, so the benefit of a timed attempt is likely to be limited.

Is a smoker's behaviour positively or negatively reinforced?

The normal neurophysiological functioning for someone having undergone considerable receptor upregulation and dependence development may be to keep some of the receptors blocked or desensitised, and heavy smoking at

regular intervals achieves this. Such smokers may not admit to any positive effects from smoking; rather, they cannot give it up because they suffer strong cravings that can only be relieved by smoking. The neuropharmacological objective for heavy smokers is to keep their nicotine concentration sufficiently high so that withdrawal symptoms do not occur.

With less upregulation the smoker would become less tolerant and therefore experience less withdrawal. Smokers less sensitive to nicotine, with probably less receptor upregulation and tolerance, may have their receptors in a more sensitised state, making the brain more susceptible to stimulation by nicotine. That may result in somewhat different pharmacological effects. In mice, stimulation of receptors by injection of nicotine produces an increase in dopamine turnover in the mesolimbic brain centres, which slower infusion does not [9]. Cigarette smoking habits that cause sharp changes in nicotine concentrations in arterial blood will affect the receptor stimulation that, in turn, may be necessary for subjective positive effects such as mood alteration and performance improvement. The rapid fall in concentrations after smoking a cigarette makes receptors sensitive again, a state necessary for restimulation.

How may these two types of smoker differ? It is reasonable to distinguish smokers who experience positive reinforcement (PR) from those with negative reinforcement (NR) according to the strength of any positive effects. It seems likely that smokers with PR will report smoking as more pleasurable, and that smokers who maintain a sufficient blood nicotine concentration to keep some receptors blocked are smoking predominantly for withdrawal relief; i.e. negative reinforcement. Those smokers who achieve sharp increases in nicotine concentrations may experience more stimulation or positive effects from the nicotine; i.e. positive reinforcement. This implies that smokers with PR would have fewer withdrawal symptoms when quitting smoking than smokers with NR who smoke mainly to avoid withdrawal symptoms. Smokers with PR may smoke at less regular time intervals than smokers with NR. If gradients (peaks) were important for subjective positive effects, it would be natural to smoke fewer cigarettes per day, to achieve a lower trough level from which it would be easier to obtain a peak. Further, to experience peaks it may be more common for smokers with PR to smoke several cigarettes sequentially. The Michigan nicotine reinforcement questionnaire has recently been proposed as a measure of PR and NR smoking [46].

Implications

Nicotine is probably the world's second most-used drug after caffeine. It has generally met very little resistance when introduced into our societies and was not regarded as a drug until recently. In psychoactive and dependence-producing drug use, people normally see behavioural changes in individuals, both when they take the drug and when try to abstain from it. Nicotine's psychotoxic effects – stimulating and tranquilising – are so mild that they are difficult to observe. Unlike most other drugs, it does not impair performance in judgement, cognition or motor behaviour. On the contrary, nicotine may slightly improve some performances and help people to cope with daily stress; it is possible that use of nicotine will diminish but unlikely that nicotine use can be totally abandoned. Our societies are fighting against illegal drugs with more profound psychotoxicity. It is therefore important that societies adopt regulatory systems [47] for safer administration of forms of nicotine, alternative nicotine delivery systems [48] and restrict tobacco smoking [49].

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