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The Effects of Nicotine on Neural Pathways Implicated in Depression: A Factor in Nicotine Addiction?

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BALFOUR, D. J. K. AND D. L. RIDLEY. *The effects of nicotine on neural pathways implicated in depression: A factor in nicotine addiction?* PHARMACOL BIOCHEM BEHAV **66**(1) 79–85, 2000.—The prevalence of tobacco smoking varies considerably between different groups within the community, tobacco smoking being particularly prevalent in patients with depressive disorder. This review will focus on results, derived from animal studies, which suggest that, in addition to its primary reinforcing properties, nicotine also exerts effects in stressful environments, which may account for its enhanced addictive potential in depressed patients. It focuses on the evidence that depression sensitises patients to the adverse effects of stressful stimuli, and that this can be relieved by drugs that stimulate dopamine release in the forebrain. This mechanism, it is proposed, contributes to the increased craving to smoke in abstinent smokers exposed to such stimuli, because they become conditioned to use this property of nicotine to produce rapid alleviation of the adverse effects of the stress. The review also explores the possibility that chronic exposure to nicotine elicits changes in 5-HT formation and release in the hippocampus which are depressogenic. It is postulated that smokers are protected from the consequences of these changes, while they continue to smoke, by the antidepressant properties of nicotine. However, they contribute to the symptoms of depression experienced by many smokers when they first quit the habit. © 2000 Elsevier Science Inc.

Nicotine dependence Depression Mesolimbic dopamine Hippocampal 5-HT

IT is now widely accepted that a large majority of habitual tobacco smokers become addicted to the nicotine present in tobacco smoke, and that this addiction plays a pivotal role in maintaining the tobacco smoking habit (9,86). The neural mechanisms underlying the development of nicotine dependence remain to be established. However, a number of studies have shown that nicotine stimulates the dopamine (DA)-secreting cells that project from the ventral tegmental area to limbic structures such as the nucleus accumbens and prefrontal cortex (21,55,67). Stimulation of the projections to the nucleus accumbens has been implicated in both the locomotor stimulant properties of the drug and its ability to reinforce self-administration in experimental animals (31,36,37,60). Other studies suggest that the DA projections to the nucleus accumbens may be an important component of the "reward pathways" of the brain (43,88), although, more recently, it has been proposed that they may be involved more specifically in incentive learning or the attribution of incentive salience to the cues and behaviours associated with administration of addictive drugs (22,41,42). Irrespective of their specific role, it is widely believed that these pathways play a pivotal role in the development of dependence to psychostimulant drugs, including nicotine.

The prevalence of tobacco smoking is much higher in people suffer from depression (26,39). These observations imply that factors other than simple reward may also play an important part in the mechanisms that reinforce nicotine self-administration and lead to dependence. The primary aim of this review is to focus on the role that depression may take in the aetiology underlying the reinforcing properties of tobacco smoke, and to advance an hypothesis that seeks to explain the neurobiology underlying the role of depressive disorder in nicotine dependence and relapse. There are two ways in which depression could play an important role in addiction to tobacco smoke. First, nicotine, or some other component of

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the smoke, may ameliorate the symptoms of depression in people who suffer from this condition. As a result, the reinforcing properties of tobacco smoke may be enhanced in smokers with an underlying depressive disorder. Second, chronic exposure to tobacco smoke may elicit changes in the brain that cause the symptoms of depression experienced by many abstinent smokers when they first quit the habit and avoidance of this, and other symptoms of withdrawal, also serve to reinforce the addiction (54,79). This review will summarise data that are consistent with the possibility that both mechanisms may be involved in nicotine dependence.

It has been reported that tobacco dependence is positively related to the severity of the depressive illness, patients with major depressive disease being more likely to become smokers and to become more heavily dependent than smokers who do not have an underlying depressive disorder (26). These authors, however, emphasised that their data did not necessarily support the conclusion that tobacco smoke alleviated the symptoms of the condition. Indeed, they suggested that it was equally likely that the association might reflect a common genetic basis for depression and tobacco dependence. Others, however, have suggested that tobacco smoke does exert an antidepressant effect (4,47), and that self-medication for depression might be an important component for addiction not only to tobacco but also to other drugs of abuse (63).

THE ANTIDEPRESSANT PROPERTIES OF TOBACCO SMOKE

It is difficult to evaluate the antidepressant properties of nicotine in tobacco smokers because it is difficult to separate the antidepressant effects per se from the alleviation of the depression that follows nicotine withdrawal. There is some evidence, however, that the administration of nicotine from a transdermal nicotine patch can exert antidepressant-like activity in nonsmokers (80). In addition, the constant infusion of nicotine to experimental rats attenuates learned helplessness, a putative behavioural model for depression (82). These data are consistent with the possibility that nicotine has antidepressant properties. The situation is confused, however, by the fact that nicotine also seems to exert effects that are inconsistent with it having antidepressant properties. Many patients with depressive disorder have high resting levels of plasma cortisol and a blunted response to the effects of dexamethasone on plasma cortisol, and there is evidence that these changes may be relevant to the neuropathology underlying the condition (12). In animal studies, unavoidable stressors have also been used in experimental paradigms, such as the Porsolt test (77), designed to explore the neurobiology underlying depression. Acute injections of nicotine increase plasma corticosterone in rats (14). Repeated daily administration of the drug for 5 days or more, however, elicits complete tolerance to this effect in unstressed rats and, in these tolerant animals, nicotine withdrawal elicits a modest increase in plasma corticosterone (14). Acute exposure to an unavoidable stressful stimulus, an elevated open platform, also causes increased plasma corticosterone (11,15). With repeated exposure to the procedure, habituation of the response is observed, although this may take up to 20 daily trials to develop fully (15). Tolerance develops more quickly and more completely in animals treated chronically with the anxiolytic drug, diazepam, whereas its withdrawal results in a rebound increase in plasma corticosterone to concentrations similar to those found in drug-naive animals tested acutely in the apparatus (34). In contrast, the administration of nicotine prior to each session in the stressful environment attenuates habituation of the plasma corticosterone response to the procedure (15). Thus, in this procedure, nicotine seems to exert effects on plasma corticosterone that are more consistent with it having anxiogenic or depressogenic properties. This is, perhaps, surprising because there are reports that systemic nicotine may have anxiolytic activity in some tests (27,38,46). Other studies, however, using doses similar to those used in our chronic stress studies, have failed to find that systemic nicotine has anxiolytic properties similar to those of diazepam (10,69). Anxiogenic responses have been observed when somewhat higher doses are given (46). It seems reasonable to suggest, therefore, that the mechanisms underlying the putative anxiolytic properties of nicotine differ significantly from those that mediate the responses to benzodiazepine-like drugs, and are not associated suppression of the adrenocortical response to stressors.

The acute administration of a high dose of nicotine stimulates the release of 5-HT in the frontal cortex of the rat (78). The putative role of this effect in the neurobiology underlying tobacco smoking is, perhaps, doubtful, because there is evidence that the administration of high doses of nicotine are anxiogenic (46) and could be expected to stimulate the neurones in the dorsal raphe, which project to this area of the brain (51). In contrast, both the acute and repeated administration of a lower dose of nicotine decrease the overflow of 5-HT into the dorsal hippocampus (Fig. 1). Other studies in our laboratory have shown that the acute and chronic administration of nicotine to experimental rats decrease the biosynthesis of 5-HT in the hippocampus, but not in the brain as a whole (16), and that chronic treatment with the drug evokes a regionally selective reduction in the concentrations 5-HT and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in the hippocampus (14). Additionally, chronic treatment with the drug causes a regionally selective reduction in the density of tryptophan transporters located on nerve terminals in the hippocampus (16). Although the mechanism by which nicotine exerts these effects on hippocampal 5-HT remain to be established, the data imply that chronic nicotine elicits a repetitive or sustained reduction in 5-HT formation and overflow in the hippocampus, and that the pathway involved in the biosynthesis of the amine in the hippocampus adapts to the reduced demand for 5-HT in this area of the brain. The putative relevance of these observations in experimental animals to our understanding of the neurobiology underlying the role of nicotine in the tobacco smoking habit is demonstrated by the fact that postmortem studies with human tissue have shown that habitual tobacco smoking is also associated with regionally selective reductions in the concentrations of 5-HT and 5-HIAA in the hippocampus (19). In addition, there is indirect evidence that this effect is associated with sustained or repetitive reductions in extracellular 5-HT in this area of the brain because the density of 5-HT_{1A} receptors is also reduced in the hippocampus of habitual smokers but not the other brain regions examined. It seems reasonable to suggest, therefore, that the nicotine inhaled in tobacco smoke exerts similar effects on the 5-HT projections to the hippocampus to those observed in rats treated with pure drug (19).

The 5-HT-secreting neurones in the dorsal raphe nuclei, which innervate limbic areas of the brain, such as the prefrontal cortex and amygdala, are stimulated preferentially by anxiogenic or stressful stimuli and inhibition of this response may mediate the therapeutic properties of benzodiazepine anxiolytic drugs (51). The hippocampus, however, receives its primary serotonergic innervation from the median raphe nucleus, this nucleus providing the sole serotonergic innervation

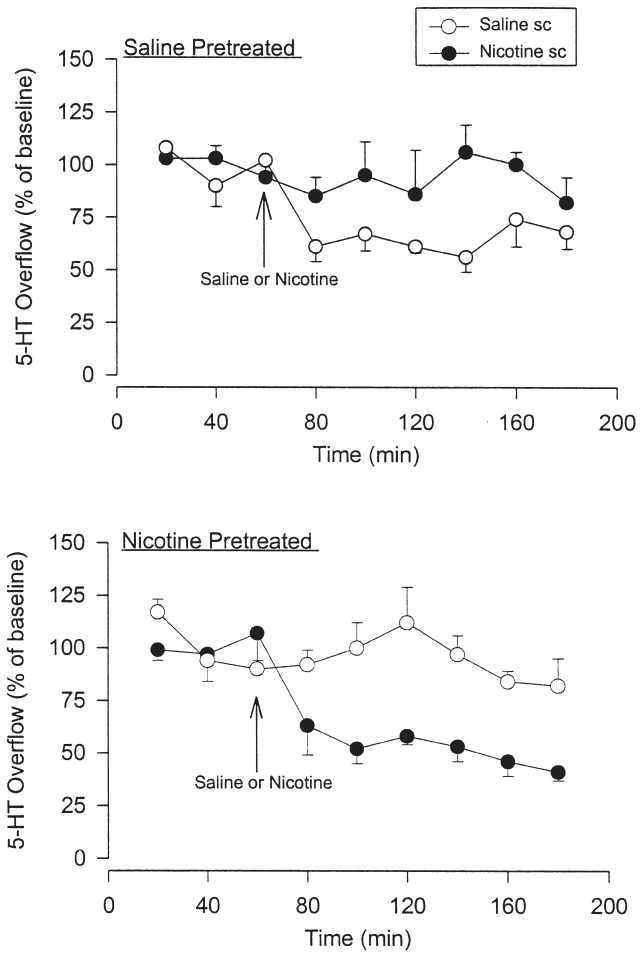

FIG. 1. The effects of systemic nicotine on 5-HT overflow in the dorsal hippocampus of the rat. Groups of male Sprague–Dawley rats ($n = 5$ per group) were placed individually into "shoebox" cages 14 days before the beginning of the experiment to habituate them to their home cages. They were then given 20 daily injections of saline or (−)nicotine (0.4 mg/kg SC). Three hours after the last injection on day 20, dialysis probes were inserted into the dorsal hippocampus under Halothane anaesthesia using the coordinates 5.2 mm posterior and 2.5 mm lateral to bregma and 3.1 mm vertical from the surface of the brain, according to Paxinos and Watson (70). Dialysis studies were performed in the rats on the following day while they remained in their home cages. Dialysis medium (NaCl; 146 mM; $CaCl_2$: 1.25 mM; KCl: 4 mM) was pumped through the probe at a rate of 1.7 μl/min. Following a period of equilibration (2 h), 3 × 20 min samples were collected before the rats were given a subcutaneous injection of saline or nicotine (0.4 mg/kg) at the time shown by the arrow in the diagram. Six further 20-min samples were collected following the injection. The samples were analysed by HPLC with electrochemical detection. The data are expressed as percentages of the mean baseline concentration of 5-HT measured in the three samples collected before the injection and are presented as means ± SE mean. The data were analysed by analysis of variance for repeated measures with pretreatment prior to the test day and treatment on the test day as the main factors analysed. Nicotine pretreatment did not exert a significant effect on baseline levels of 5-HT in the dialysates (0.014 ± 0.010 pmol/20 μl for saline-pretreated rats and 0.016 ± 0.011 pmol/20 μl for the nicotine-pretreated rats). The effect of a nicotine injection on the test day was significant [treatment × time, $F(8, 128) = 4.43$, $p < 0.001$]. Pretreatment with nicotine had no significant effect on the response to the drug on the test day.

to the dorsal hippocampus (5). There is now evidence that these neurones may also be implicated in the expression of anxiety. For example, Andrews and colleagues (3) have reported that the anxiety associated with the withdrawal of benzodiazepines, following a period of chronic treatment, is mediated by increased 5-HT release from these neurones. Suppression of 5-HT release in this part of the hippocampus may also explain the anxiolytic response to nicotine, observed when the drug is given locally by microinjection into the dorsal hippocampus (69), although this requires confirmation. Alternatively, it has been proposed that the projections to the dorsal hippocampus from the median raphe nucleus play a pivotal role in promoting resistance to chronic unavoidable stressors, and that impaired activity or plasticity in this pathway may contribute significantly to the neuropathology of affective disorder (40,69). This conclusion is consistent with the results of recent dialysis studies in our laboratory (Petrie and colleagues, unpublished observations) in that they show that repeated exposure to an unavoidable stressor causes an increase in 5-HT overflow in the dorsal hippocampus that is not apparent in rats exposed acutely to the stressor. These data suggest that increased 5-HT overflow in the dorsal hippocampus may be an adaptive response to repeated exposure to the stressor.

The expression of the receptors for corticosterone in the hippocampus is regulated potently and predominantly by occupation of 5-HT receptors in this area of the brain (81,89). These receptors are thought to play an important role in facilitating attenuation or habituation of the plasma corticosterone response to stress (23,24,64). Thus, it seems reasonable to suggest that the primary physiological role of the increase in 5-HT release evoked by repeated exposure to a stressor is to facilitate the expression of the receptors for corticosterone in the hippocampus and, thus, habituation of the response to the stressor. If this is the case, then the inhibitory effects of nicotine on 5-HT release from these projections would serve to attenuate habituation to such a stressor and, thus, mimic an important element of the neuropathology thought to underlie depressive disorders. This conclusion is consistent with results from our laboratory that have shown that chronic nicotine attenuates habituation of the plasma corticosterone response to an unavoidable stressor, and that the nicotine-treated animals that habituate least have the lowest concentrations of 5-HT in the hippocampus (15). In contrast, in saline-treated rats, the animals that habituate least have the highest concentrations of 5-HT in this area of the brain. These results imply that the effects of nicotine on plasma corticosterone and hippocampal 5-HT are more consistent with those of a drug that causes depression rather than those of a drug that alleviates the condition and are, therefore, unlikely to be the mechanism underlying the proposed antidepressant properties of the drug.

The symptoms of depression can be alleviated by drugs that do not act directly on 5-HT synapses. For example some patients respond very favourably to compounds, such as reboxetine, which, at therapeutic doses, preferentially inhibit the presynaptic transporter for noradrenaline (29). Because nicotine stimulates noradrenaline release in the brain (18,65), its effects of nicotine on the release of this transmitter are consistent with an antidepressant response to the drug.

An alternative possibility is based on the evidence that the anhedonia, associated with depressive disorder, may be related to reduced DA release in the mesolimbic system, and that this is reversed by chronic treatment with antidepressant drugs (56). This conclusion is supported by results that have shown that chronic treatment with antidepressant drugs with

differing mechanisms of action at the molecular level sensitise the mesolimbic DA system to the effects of amphetamine on DA overflow in the nucleus accumbens and the effects of amphetamine and DA receptor agonists on locomotor activity (32,57,62,67,74,85). Repeated exposure to electroconvulsive stimulation (ECS) exerts a similar effect (68). Pretreatment with tricyclic antidepressants or ECS increases both DA overflow in response to amphetamine (67,68) and the postsynaptic response to DA agonists (57,61,85). In contrast, serotonin selective reuptake inhibitors preferentially enhance postsynaptic responses to DA in the terminal fields of the mesolimbic system (2,32). Nicotine also stimulates DA release from mesolimbic neurones (55,67), and there is evidence that chronic exposure to the drug can result in sensitisation of its effects on DA overflow in the nucleus accumbens when measured using dialysis (8,17,18). In addition, pretreatment with nicotine also sensitises rats to the locomotor stimulant properties of D-amphetamine, although this response is not associated with sensitisation of the effects of amphetamine on DA overflow in the accumbens (25). The data are more consistent with the hypothesis that sensitisation of locomotor activity, evoked by nicotine, reflects an enhanced response to DA at the postsynaptic level (25). Thus, the effects of repetitive nicotine administration on mesoaccumbens DA neurones have significant similarities with those of antidepressant drugs.

In experimental animals, exposure to stressful stimuli promotes the acquisition of drug self-administration of many drugs of abuse (72). These data have been interpreted as evidence that stress enhances the reinforcing efficacy of these compounds. Although the effects of stress on nicotine self-administration have not yet been studied, there is evidence that nicotine can ameliorate the effects of stress on other behaviours. For example, it preferentially attenuates the suppressant effects of a stressor on locomotor activity (87) and facilitates the acquisition and performance of a stressful shock avoidance task (66). The withdrawal of nicotine from rats, trained to perform this task in the presence of the drug, causes a decrement of avoidance performance to a level that is significantly worse than that of control rats trained with saline (66). This has been interpreted as evidence that rats, trained on this type of schedule with nicotine, become dependent upon the drug for successful performance of the task. Subsequent studies have shown that similar significant decrements of performance are observed in rats trained to perform the task after injections of D-amphetamine, and that D-amphetamine can ameliorate the deficits in performance observed following nicotine withdrawal (6). Although it is necessary to be cautious about the interpretation of the results because they could simply be a reflection of the locomotor stimulant properties of the drugs, other studies have shown that the performance of rats trained on a shock avoidance schedule is very sensitive to disruption by DA receptor antagonists (59). Thus, the data are consistent with the possibility that the rats become dependent upon enhanced DA release to perform a task in a stressful environment.

Piazza and Le Moal (71) have proposed that one of the functions of increased DA release in the forebrain is to counteract adverse effects of stressful environmental stimuli on behaviour, and that this mechanism explains the influence of stress on the addictive potential of drugs of abuse. Intravenous injections of nicotine elicit a rapid increase in DA release in the nucleus accumbens (76). A similar response could also be expected of nicotine inhaled in tobacco smoke because, when taken in this way, it reaches the brain very rapidly (13). It has been known for some time that exposure to stressful stimuli enhances the craving to smoke (50,75). More recently, it has been shown that exposure to a stressor reinstates responding for nicotine following its extinction in drug-free animals (28). These data support the conclusion that stress can act as a stimulus for nicotine self-administration, although it is important to acknowledge that it is not specific to this drug, similar effects being observed in animals trained to respond for heroin (83), cocaine (1), or ethanol (58). However, the potential for developing associations between stressful environmental stimuli and tobacco smoking may be particularly strong because of the repetitive nature of the habit.

The data summarised above suggest that the putative ability of nicotine to ameliorate the adverse effects of stress may be related, in part at least, to its stimulatory effects on catecholamine release in the brain. In the context of the tobacco smoking habit, however, this hypothesis must be treated with some caution, because it is based on the results of studies in which the responses to nicotine reflect stimulation of neuronal nicotinic receptors. There is electrophysiological evidence, however, that the neuronal nicotinic receptors expressed on DA-secreting neurones in the ventral tegmental area can be desensitised by prolonged exposure to nicotine at doses commonly found in the plasma of smokers (73). This observation is consistent with the results of in vivo microdialysis studies that have shown that the stimulatory effects of a nicotine injection on DA release in the nucleus accumbens are abolished in rats constantly infused with nicotine at a rate that also maintains the plasma nicotine concentration within the range found in many habitual smokers (20). Other studies have also shown that nicotine infusions also attenuate the stimulation noradrenaline release in the hippocampus evoked by a nicotine injection (18). This is significant because the study by Semba and colleagues (82), which demonstrated the putative antidepressant properties of nicotine in an animal model for the condition, employed constant infusions of the drug at a dose that desensitises its effects on DA and noradrenaline release. In these animal experiments, nicotine was delivered as a constant infusion that does not closely mimic the changes in blood nicotine that will occur as smokers inhale each puff of cigarette smoke or the variations in the "basal" plasma nicotine concentration that occur through the day (13). Nevertheless, it is unlikely that stimulation of DA or noradrenaline release accounts for the response observed by Semba and colleagues, and that a different mechanism, possibly involving stimulation of an isoform of the neuronal nicotinic receptor that does not readily desensitise, may need to be invoked to explain the proposed antidepressant properties of nicotine.

The administration of a nicotinic receptor antagonist to animals constantly infused with nicotine, precipitates behavioural changes that are thought to model the nicotine abstinence syndrome and decreases DA overflow in the nucleus accumbens (52). The changes in DA overflow have been interpreted as a neural correlate of the anhedonia or dysphoria experienced by smokers when they quit the habit. Epping-Jordan and colleagues (45) have also reported that nicotine withdrawal, following a period of constant infusion, decreases the rewarding effects of intracranial self-stimulation. The results imply that, following a period of constant exposure to the drug, mesoaccumbens DA neurones may become dependent upon nicotine to maintain normal levels of activity. These data provide support for the hypothesis that reductions the plasma nicotine concentration, following a period of chronic exposure, may elicit an anhedonic state that a smoker might seek to avoid by continuing to smoke.

It also important to remember that tobacco smoke contains

other components that might have antidepressant properties. Of particular significance is the evidence that tobacco smoke contains a compound or compounds, almost certainly not nicotine itself, which inhibit monoamine oxidase (47–49). This effect has been implicated in the proposed antidepressant properties of tobacco smoke, and it has been suggested that it contributes to the high rates of smoking in depressed individuals (47).

THE ROLE OF DEPRESSION IN NICOTINE DEPENDENCE: A WORKING HYPOTHESIS

The evidence for an association between depressive disorder and the prevalence of tobacco smoking is consistent and robust. The data do not exclude the possibility that this reflects commonalities in the genetic and environmental factors that underlie a predisposition to depression and nicotine dependence (26). It is also possible that an underlying depressive disorder enhances the "rewarding" properties of addictive drugs in a way that does not depend upon alleviation of the symptoms per se. However, this review has outlined evidence that nicotine has antidepressant-like properties that could also account for the association. In addition, there is evidence that nicotine interacts with neural mechanisms that respond to the types of stressor that have been used to model depression in experimental animals. It seems reasonable to suggest, therefore, that the association does reflect a capacity to alleviate symptoms of depression or, at least, the adverse consequences of the condition on the responses to stressful stimuli.

The data available suggest that two independent mechanisms may be involved. The first depends upon the maintenance of a relatively high plasma nicotine concentration at a level that causes desensitisation of the nicotinic receptors present on mesolimbic DA-secreting neurones (18,20,73). This possibility is consistent with the observation that the constant infusion of nicotine elicits an antidepressant-like action in rats (82), and the fact that severe depressive disorder is often associated with high levels of smoking (26). However, the results imply that, for periods when the plasma nicotine concentration is maintained at a relatively high concentration, direct stimulation of DA release in the nucleus accumbens is unlikely to be the primary mechanism underlying the reinforcing properties of tobacco smoke. At these times it seems reasonable to suggest that other psychopharmacological properties of nicotine, including its ability to alleviate depression, may be more relevant and serve to reinforce high levels of smoking behaviour in subjects with an underlying depressive disorder.

The second mechanism is invoked when the plasma nicotine concentration is low, following a period of abstinence for instance, when the receptors on catecholamine-secreting neurones are not desensitised. It is based on the evidence that, in addition to its primary role in reinforcement, the stimulation of DA release in the forebrain also has the potential to alleviate the adverse effects of stressful stimuli on behaviour and to promote the self-administration of addictive drugs. It proposes that the increase in DA release evoked in the nucleus accumbens by the nicotine present in the smoke provides a rapid means of alleviating the adverse psychophysiological effects of the stressor and that, with repetition, the desire to smoke can become a conditioned response to stress. This is consistent with the evidence that exposure to stressful stimuli enhances the desire to smoke, increases relapse in abstinent smokers (44,50,84) and reestablishes responding for nicotine in experimental animals (30). Interestingly, sensitised mesolimbic DA responses can be observed in nicotine-withdrawn animals following either repetitive injection of the drug or its constant infusion at a dose similar to that which appears to exert an antidepressant-like action (17,20). An important tenet of the hypothesis is that depressive disorders often sensitise patients to the effects of environmental stressors or exacerbate their effects. As a result, this conditioned response may develop more readily and more powerfully in depressed individuals. This argument is consistent with the self-medication theory proposed by Markou and colleagues (63). Our data suggest, however, that even in the absence of an underlying depressive disorder, chronic exposure to nicotine elicits changes in hippocampal 5-HT and adrenocortical function, which are characteristic of depression. The hypothesis predicts that smokers are "protected" from the adverse consequences of these changes while the continue to smoke, but that they contribute significantly to the symptoms of depression experienced by many smokers when they stop smoking (54,79). These may related to the reduction in brain reward function observed in nicotine-withdrawn rats (45). If this is the case, then it implies that, in most smokers, nicotine withdrawal may elicit a state in which they are more sensitive to the adverse effects of stress, and that exposure to such stimuli will enhance the craving for nicotine.

THE ROLE OF ANTIDEPRESSANT DRUGS IN THE TREATMENT OF SMOKING CESSATION

A corollary to the hypothesis proposed above is that antidepressant drugs may have some value in treating the symptoms of smoking cessation. This is not a new idea (7), and a number of drugs, with different mechanisms of action, have been investigated. Selective 5-HT reuptake inhibitors reduce smoking in patients with major depressive disorder, but appear to have little effect on cessation rates in the general population (4,35). These observations support the hypothesis that coexisting depressive disorder increases the dependence on tobacco, and that its treatment diminishes the desire to smoke. It is possible that drugs that potentiate the effects of 5-HT in the brain may be more efficacious in the treatment of smoking cessation more generally if they are started some weeks prior to stopping smoking (4). However, recent reports suggest that antidepressants, such as bupropion, may be more effective treatments for smoking cessation (53). This compound potentiates the effects of noradrenaline and DA in the brain (33). It is possible, therefore, that the ability to potentiate the effects of brain DA is fundamental to the efficacy of bupropion in the treatment of nicotine withdrawal. It is based on the hypothesis that the craving for nicotine can be ameliorated by drugs that maintain raised extracellular DA levels in the brain, particularly when the craving is enhanced by exposure to a stressor. This is consistent with the hypothesis, proposed in this review, that predicts that smokers may become dependent upon the stimulatory effects of nicotine on DA release in the brain to cope with stressful stimuli, and that this conditioned response contributes significantly to the craving to smoke in abstinent smokers. This conclusion points to an exciting new direction in our understanding of the pharmacology underlying nicotine dependence and the factors that precipitate craving and relapse in abstinent smokers. Clearly, however, this and other aspects of the working hypothesis proposed require further detailed investigation.

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