

Research on stress and smoking: progress and problems

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Abstract

Despite evidence that smoking behaviour increases in the context of stress, there has yet to be a clear-cut demonstration that nicotine intake is similarly enhanced. Although nicotine intake has been shown to reduce reported anxiety in the context of stress, the controlling conditions (type of stressor, intensity, temporal relationships, etc.) need further exploration. Recent findings involving nicotine's effects on the hypophyseal-adrenal axis provide a new perspective on these issues, in that increased nicotine intake during exposure to a stressor may represent, at least in part, behavioral compensation for diminished sensitivity to nicotine brought about by nicotine-stimulated corticosteroid release. Corticosteroids may decrease central nervous system excitability in a way that could account for anxiety reduction; on the other hand, anxiety reduction may be an epiphenomenon with respect to the reinforcement of smoking behaviour. The integration of behavioural, physiological, and biochemical research exemplified by the above approach should lead to a better understanding of stress and smoking.

Introduction

The relationship between stress and smoking, and a corresponding link between smoking and anxiety reduction, are so well entrenched in the lore concerning cigarette smoking (see USDHHS, 1988, pp. 394-414) that they have assumed the status of truisms. A critical examination of the support for these relationships is timely because (a) much smoking does seem to occur in response to stress, (b) relapse after quitting appears to be strongly associated with dysphoric states, and (c) commonalities in the neuroendocrine response to nicotine and to stress suggest that a study of interactions may yield useful knowledge about both phenomena. In this brief review, we shall examine questions that we believe must be addressed more systematically if further progress is to be made. Key issues include: (1) The relationship between stress and smoking—is it real or apparent? (2) What are the controlling conditions for anxiety reduction in the reinforce-

ment of smoking? (3) What are the biological mechanisms entrained by smoking in the context of stress, and how do they contribute to subjective and behavioural phenomena?

The relationship between stress and smoking

Smokers commonly report smoking more under conditions experienced as stressful, and it has been suggested that smoking is a technique for dealing with stress. Prospective studies have found associations between anxious, aggressive, and generally neurotic personality traits in childhood and a tendency to smoke later in life. Using a cross-sectional sample of 668 adults, Billings & Moos (1983) found that smokers, especially heavy smokers, differed from non-smokers in showing higher levels of anxiety/depression symptoms and negative life events.

Analysis of the circumstances surrounding recidivism supports the stress-smoking link. In a prospective study of predictors of outcome in 100 treated smokers, Pomerleau *et al.* (1978) found that relapse was predicted by the smoker's identifying 'negative affect' as the context in which smoking was most likely to occur. Similarly, Shiffman (1982) found that most relapse crises in ex-smokers who utilized the services of a relapse-counseling 'hotline' were associated with negative affect, particularly anxiety (which was twice as frequent as the next most common antecedent affect); in over half of the crisis episodes, no other nicotine withdrawal symptoms were reported.

Laboratory studies have strengthened the inference of a causal link between stress and smoking. Schachter (1978) showed in a series of studies that naturalistic stressors such as public speaking, simulated airplane noise, and electric shocks were associated with sharp increases in smoking, as measured by number of cigarettes lighted up. Other experimenters (Dobbs *et al.*, 1981; Pomerleau & Pomerleau, 1987; Rose *et al.*, 1983) have also reported increased smoking in response to stress, using more precise measures of smoking topography. A definitive demonstration that psychological stress reliably increases nicotine intake, however, has yet to be reported. What will be needed are well-controlled studies that include measures of plasma nicotine and explore systematically parameters relating to the nature and timing of the stressor. Also needed is an investigation of the possibility that a disjunction between nicotine intake and smoking behavior exists (and that observed increases in smoking represent a form of adjunctive behavior rather than increases in nicotine self-administration). Larger studies focusing on individual differences will be required to determine whether stress induction of smoking is more pronounced in some people than in others.

The controlling conditions for anxiety reduction from smoking

Reduction of anxiety via nicotine self-administration is the principal hypothesis offered to explain reinforcement for smoking in the context of stress. Nesbitt (1973) and Silverstein (1982) reported that aversive shock thresholds increased in proportion to the nicotine content of cigarettes smoked; Silverstein (1982) speculated that this phenomenon was a manifestation of anxiety reduction caused by nicotine, but no measurement of either nicotine intake

or changes in anxiety was made. Other studies have indicated more direct effects of smoking on dysphoric mood states. For instance, Schachter (1978) reported that heavy smokers were more irritable during exposure to simulated plane overflights when they were totally deprived of smoking or smoked low nicotine cigarettes. Smokers who smoked high nicotine cigarettes, however, were no less irritable than non-smokers exposed to the same stressor. In another study using noise stress, Woodson *et al.* (1983) also found that anticipatory smoking diminished self-reported anxiety.

Pomerleau *et al.* (1984) reported smoking-related reductions in cold-pressor pain and in anxiety generated in anticipating presentation of a difficult anagram. A subsequent study involving only cold-pressor pain (Fertig *et al.*, 1986) demonstrated these effects to be dose-related, both in minimally-deprived smokers and ex-smokers. These findings, combined with related research with nicotine-naive animals, support the existence of nicotine effects independent of relief of nicotine withdrawal. The definitive test at the human level, however, will require administration of nicotine to never-smokers.

Jarvik *et al.* (1989) recently examined anticipatory anxiety for four stressors: Anxiety generated by anticipation of auditory vigilance or of white noise was not reduced by smoking and anxiety in anticipation of cold pain was marginally reduced, whereas anxiety in anticipation of a difficult anagram was significantly dampened by smoking. Uncontrolled factors that may have contributed to these effects include sensory modality and social context (subjects were observed during the anagram and cold pain conditions but not the vigilance and white noise conditions) as well as relative intensity. Jarvik speculated that the temporal relationship between the stressor and smoking was important, since even when smoking diminished pre-task anxiety, post-task anxiety was not affected. Subsequent research by Jarvik and colleagues (Caskey, personal communication, 1990) has indicated that when it does occur, anxiety reduction following smoking is transitory, coinciding with the sharp rise in plasma nicotine. Thus, the phenomenon of anxiety-reduction may be limited to a brief period following smoking. A limitation of this and other studies of anxiolysis of nicotine carried out to date is that nicotine was self-administered, typically via cigarette smoking. Controlled dosing methodologies that are less dependent on drug-ingestive behaviors such as inhaling, snuffing, etc. are essential to prevent behavioral compensation in response to nicotine

deprivation, satiation, stress, demand characteristics, etc. (Pomerleau *et al.*, 1989).

Biological mechanisms in smoking and stress

Although progress has been made, the elusiveness of the relationship between stress and smoking suggests that new paradigms identifying underlying biological mechanisms will be needed if we are to extend our understanding of this phenomenon. Schachter (1978) offered an early alternative to the anxiety-reduction hypothesis; noting that acidification of urine by a stressor increases nicotine excretion, he speculated that the resulting nicotine withdrawal might be perceived as anxiety and compel replacement of nicotine by increased smoking. This explanation had some appeal, since it obviated the necessity of relying exclusively on an intervening variable—anxiety—that was hard to define and measure; but subsequent parametric experimentation manipulating urinary pH (Rosenberg *et al.*, 1980) failed to support the hypothesis. Recent work by Winders (personal communication, 1990), however, demonstrated significantly lower blood nicotine levels in rats exposed over 2.5 hours to psychological and physical stressors than in unstressed animals. These findings suggest that prolonged or severe stress could diminish nicotine availability, resulting in withdrawal and presumably in compensatory intake.

We have recently become intrigued by the possibility that the hypophyseal-adrenal axis may provide important clues for understanding stress-induction of smoking when it occurs, as well as explanatory mechanisms capable of incorporating what has been learned about anxiety reduction in smoking. ACTH, the hormone that stimulates corticosteroid release, is a hypophysical peptide under the control of corticotropin releasing hormone in the hypothalamus (see Pomerleau & Rosecrans, 1989). Nicotine, in a dose-related manner, has been shown to stimulate release of ACTH in an isolated perfused mouse brain preparation (Marty *et al.*, 1985) and, in intact rats, to increase the levels of plasma ACTH and corticosterone (the major corticosteroid for rodents) (Conte-Devolx *et al.*, 1981). Pomerleau and colleagues (Pomerleau *et al.*, 1983; Seyler *et al.*, 1984), in a series of studies on cigarette smokers, demonstrated significant, dose-related increases in circulating ACTH and cortisol following the smoking of high-nicotine cigarettes after overnight deprivation.

A series of studies recently conducted by Collins

and his colleagues has helped to characterize the relationship between nicotine and stress. Using inbred mice, Freund *et al.* (1988) demonstrated consistent strain differences in corticosteroid stimulation by nicotine; the effect was abolished by mecamylamine, substantiating the involvement of a nicotinic cholinergic receptor. Moreover, strain-specific differences in the endogenous corticosterone response were paralleled by behavioral and physiological differences in sensitivity to nicotine. Thus, individual differences in responsiveness to nicotine in mice were found to be stable and genetically based. In a study by Pauly *et al.* (1988), adrenalectomized mice exhibited greatly enhanced sensitivity to the effects of nicotine, with significant dose-related increases in acoustic startle response and decreases in Y-maze activity, heart rate, and core temperature, though nicotinic cholinergic receptor number was unaffected and nicotine metabolism unchanged. Administration of exogenous corticosterone restored protection from the effects of nicotine in the adrenalectomized animals. Administration of corticosterone to non-adrenalectomized animals further decreased sensitivity to nicotine, supporting the hypothesis that nicotine's own corticosteroid response (rather than ACTH changes, etc.) reduced the sensitivity of nicotine receptors. Collins and his associates (personal communication, 1989) have subsequently found that extended exposure to nicotine produces dose-related decreases in nicotine stimulation of corticosterone, indicating that the nicotinic receptor involved in corticosteroid regulation is also subject to diminution of sensitivity as a result of chronic dosing.

To determine whether similar effects might occur in humans, we manipulated corticosteroid levels by administering dexamethasone (a synthetic corticosteroid) and used magnitude of cortisol stimulation by nicotine as a marker of sensitivity to nicotine (Pomerleau & Pomerleau, 1990). As hypothesized, there was a significant dampening of the cortisol response to nicotine following administration of dexamethasone the night before. There was also a trend towards a significant correlation between cortisol increases for the dexamethasone and placebo conditions, suggesting characteristic individual differences in response to nicotine. We plan to replicate these observations in a larger sample of smokers, using a variety of synthetic corticosteroids and additional physiological and behavioral measures of sensitivity to nicotine.

Recently, Morse (1989) reported that restraint stress and repeated acute nicotine dosing produce

additive effects upon circulating corticosterone in rabbits. Again, to determine whether psychological stress and nicotine administration via smoking might also produce additive effects in humans, we exposed moderate smokers to stress and/or nicotine in four successive sessions (Pomerleau & Pomerleau, 1990). Cortisol levels were elevated by smoking and by stress separately, and the two in combination had an additive effect, suggesting that psychological stressors exacerbate the corticosteroid response to nicotine, potentially reducing sensitivity to nicotine still further.

Although the research on corticosteroids described above is still preliminary, we believe that it shows potential for increasing our understanding of various smoking-related phenomena. The demonstration that nicotine and/or stress cause corticosteroid release provides a novel way of explaining interactions between smoking and stress, for it suggests that increased nicotine intake during exposure to a stressor may represent, at least in part, behavioral compensation for diminished sensitivity to nicotine. While corticosteroid mechanisms might play a role in the reduction of anxiety by smoking, there is also the possibility that anxiety reduction following nicotine self-administration in the context of stress is simply an epiphenomenon, an effect frequently associated with but not critical to increased smoking behavior.

In normal humans, the initial response to an acute stressor is stimulation of metabolic, neuronal, inflammatory, and immune activity, mediated in part by adrenergic activity resulting in increased sympathetic tone and catecholamine levels. With chronic or severe stress, however, the hypophyseal-adrenocortical system is also entrained, and endogenous opioids and corticosteroids are released. According to recent theory (Munck *et al.*, 1984), stress-induced increases in corticosteroid levels function not to protect against the source of stress itself (as was originally hypothesized by Selye, 1956), but rather to set homeostatic limits on the primary defense mechanisms. The secondary (hypophyseal-adrenocortical) response to stress is sufficiently delayed in relation to the initial stress response to allow appropriate protective mechanisms to become activated. After the corticosteroids have countered the primary adrenergic response, activity of the pituitary-adrenal axis is reduced through a negative feedback process.

Nicotine administration via smoking may be adaptive on a short-term basis, increasing the availability of hormones that protect against pertur-

bations from the primary stress-response. On the other hand, if both stress and nicotine act via the same or a related population of receptors, then the tolerance to nicotine that develops in the chronic heavy smoker may dampen the hypophyseal-adrenal response to stress. Some support is provided by recent findings by Shiffman and Kassel (personal communication, 1990) in which occasional, light smokers ('chippers') evinced greater cortisol reactivity to the same dose of nicotine than regular, more nicotine-dependent smokers. Thus, chronic smokers may come to use smoking as a pharmacological coping response to maintain normal metabolic function in the context of stressful stimulation. Over time, however, diminished corticosteroid reactivity resulting from either chronic stress or regular nicotine intake may increase the amount of nicotine needed, thwarting the chronic smoker's attempts to achieve metabolic balance.

While the functional implications suggested above go beyond what is known unambiguously, the ideas are testable using present methodologies. Moreover, since investigation of a single system is unlikely to provide 'the' explanation for the relationship between stress and smoking, the contributions of other mechanisms, such as brain electrophysiology, altered perceptual thresholds, and hypothalamic consummatory drive reduction (USDHHS, 1988), as well as the patterns of release and turnover of other neuroregulators, such as the catecholamines, serotonin, and the endogenous opioids (Pomerleau & Pomerleau, 1984), will need to be taken into account if a comprehensive understanding of smoking in the context of stress is to emerge.

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