

Smoking, Stress, and Negative Affect: Correlation, Causation, and Context Across Stages of Smoking

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This transdisciplinary review of the literature addresses the questions, Do stress and negative affect (NA) promote smoking? and Does smoking genuinely relieve stress and NA? Drawing on both human and animal literatures, the authors examine these questions across three developmental stages of smoking—initiation, maintenance, and relapse. Methodological and conceptual distinctions relating to within- and between-subjects levels of analyses are emphasized throughout the review. Potential mechanisms underlying links between stress and NA and smoking are also reviewed. Relative to direct-effect explanations, the authors argue that contextual mediator–moderator approaches hold greater potential for elucidating complex associations between NA and stress and smoking. The authors conclude with recommendations for research initiatives that draw on more sophisticated theories and methodologies.

Nearly 25% of the U.S. population smokes tobacco despite the well-known negative consequences (Centers for Disease Control and Prevention, 1997). Although recent progress has been made in understanding factors that influence smoking and nicotine self-

administration, significant gaps remain in knowledge of why people smoke. Questions such as which specific acute interoceptive (subjective) and behavioral effects of nicotine are most reinforcing in animals and humans remain largely unanswered (Perkins, 1999b).

In stress-coping (Wills & Shiffman, 1985) and self-medication (Khantzian, 1997) models of substance abuse, drugs are thought to serve a coping function whereby they facilitate general mood regulation. There is reason to believe that some people use a diverse array of psychoactive drugs, including alcohol (Cooper, Russell, Skinner, & Windle, 1992), cocaine (Jaffe & Kilbey, 1994), marijuana (Schafer & Brown, 1991), and tobacco (Ikard, Green, & Horn, 1969) as a means of regulating their mood and coping with stress. Similarly, virtually all smokers attribute their smoking, at least in part, to its alleged anxiolytic and sedative properties (Frith, 1971; Spielberg, 1986; see also Leventhal & Cleary, 1980). As described by O. F. Pomerleau and Pomerleau (1991), “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 that they have assumed the status of truisms” (p. 599). Indeed, smokers reliably report that they smoke more when they are stressed, angry, anxious, or sad (e.g., Coan, 1973; Ikard et al., 1969; McKennell, 1970; M. A. H. Russell, Peto, & Patel, 1974; see also Shiffman, 1993), and they hold the expectation that smoking will alleviate these negative moods (Brandon & Baker, 1991; Copeland, Brandon, & Quinn, 1995). At the same time, the fact that smokers believe that smoking helps to reduce negative affect (NA) does not, in and of itself, render this a valid conceptualization. Clearly, a more thorough assessment must be undertaken to truly grasp the relationship between stress and NA and smoking.

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The importance of fully understanding the relationship between tobacco use and elevated levels of NA cannot be overestimated. Such knowledge would necessarily shape smoking prevention, treatment, and policy at multiple levels. Therefore, the goal of this article is to review stress–NA–smoking interactions from a synthesis of biopsychosocial perspectives that draws upon both animal and human research. As such, we examine the extant literature in the hope of finding better answers to the following distinct, but frequently blurred, questions: (1) Do stress and NA promote smoking and nicotine intake? Specifically, are there valid and reliable associations between affective distress and (a) smoking status (smoker vs. nonsmoker) and (b) actual cueing (prompting) of smoking? Second, even if it were established that stress and NA were linked to smoking (at either or both of these levels of analysis), this would not mean that smoking relieves stress and NA. This often ignored point leads to another, very different, question: (2) Does smoking genuinely reduce stress and NA? Moving beyond the self-report of smokers, what do experimental studies reveal regarding the influence of smoking on stress and NA? Taken together, then, the following three questions are addressed regarding smoking–affect relationships (see Table 1): (a) Do smokers and nonsmokers differ on levels of stress and NA?, (b) Do stress and NA genuinely cue smoking?, and (c) Does smoking reduce stress and NA?

SOME BASIC CONSIDERATIONS OF NICOTINE–STRESS–NA RELATIONSHIPS

Cigarette smoke contains over 4,000 known chemical compounds (U.S. Department of Health and Human Services [USDHHS], 1988), many of which may contribute to smoking's effects on the human brain and body. There is substantial evidence that nicotine is the compound most likely responsible for many of the psychological and behavioral effects of smoking, including smoking's impact on stress (O. F. Pomerleau & Pomerleau, 1991; O. F. Pomerleau & Rosencrans, 1989). Nonetheless, one must be careful not to infer that nicotine is solely responsible for stress reduction or any other effects. For example, Rose and colleagues (Levin, Rose, Behm, & Caskey, 1991; Rose, Behm, & Levin, 1993) demonstrated that smoking-related sensory cues influence regulation of smoke intake and psychological stress independently

of nicotine. Moreover, emerging evidence implicates the possible role played by other smoke constituents in modifying brain monoamine oxidase levels (Fowler et al., 1996, 1998). When trying to elucidate the associations between smoking and emotion, it is critical to differentiate smoking and all that it entails (sensory cues, behavioral actions, administration of numerous chemical compounds) from pure nicotine effects.

It should also be acknowledged that certain pharmacodynamic aspects of cigarette smoking make the study of its effects on NA and stress difficult to assess and interpret. It has been fairly well established that (a) physical dependence often plays a significant role in smoking (USDHHS, 1988); (b) negative affective states, including anxiety, dysphoria, and irritability, are among the hallmark symptoms of nicotine withdrawal (Hughes, Higgins, & Hatsukami, 1990); (c) there is marked variability in the experience and time course of withdrawal across individuals (Piasecki, Fiore, & Baker, 1998; Piasecki et al., 2000); (d) nicotine appears to often relieve these withdrawal symptoms (Hughes et al., 1984); and (e) many studies assessing subjective effects have simply compared groups of nicotine-deprived and non-nicotine-deprived smokers (e.g., Cutler & Barrios, 1988; Fleming & Lombardo, 1987). Hence, it becomes difficult to tell whether differences in NA between nicotine-deprived and non-nicotine-deprived smokers are due to withdrawal adversely affecting deprived smokers or to smoking genuinely improving mood over normal levels (see Hughes, 1991; Kalman, 2002; R. West, 1993). Although one could reasonably argue that the source of NA—be it from nicotine deprivation or other more naturally occurring emotional events—does not really matter when delineating smoking–NA relationships, we agree with Hughes (1991) and others (Kalman, 2002; R. West, 1993) that differentiating deprivation reversal from genuine affect-enhancement effects is important to both theory development and intervention efforts. Thus, in this article, we concentrate our efforts on the effects of nicotine and smoking on stress and NA in relatively minimally deprived smokers.

STUDY SELECTION CRITERIA

We conducted literature searches on PsycINFO and MEDLINE databases using the following key word algorithms: *nicotine OR*

Table 1
Three Primary Questions Addressed by Review to Determine Whether Stress and Negative Affect (NA) Promote Smoking, With Characteristics of Analysis

Study characteristic	Level of analysis		
	Between-subjects	Within-subject	
	Do smokers & nonsmokers differ on levels of stress & NA?	Do stress & NA cue smoking?	Does smoking reduce stress & NA?
Sample	Smokers & nonsmokers	Smokers only	Smokers only
Methodological approach	Epidemiological; controlled laboratory investigation	Controlled laboratory or controlled field investigation	Controlled laboratory or controlled field investigation
Applicability across smoking stages			
Initiation	Yes	Yes	Yes
Maintenance	Yes	Yes	Yes
Relapse	No	Yes	Yes

smoking AND emotion OR mood OR stress OR anxiety OR depression. These searches resulted in over 5,000 citations, the vast majority of which were false positives, as they neither directly nor indirectly addressed smoking–affect relationships. Of the remaining 1,000 or so articles, we excluded those that specifically examined the time course and symptoms of nicotine withdrawal (e.g., Piasecki et al., 1998; see also Hughes et al., 1990) in the absence of smoking, as one of our primary objectives was to determine whether smoking or nicotine or both exert a genuine beneficial effect on NA above and beyond the influence of withdrawal relief. However, because previous research suggests that some smokers smoke in part to alleviate affective withdrawal symptoms, we did consider several studies in which subjects underwent extended periods of nicotine deprivation (> 4 hr) followed by smoking in our review of the smoking maintenance and relapse stages.

Studies addressing the between-subjects question of whether smokers experience more stress and NA than nonsmokers made up the majority (~150) of the remaining articles. Of these, we included those articles that drew on nationally representative samples, had sample sizes large enough to provide adequate statistical power to detect group differences, provided operational definitions of smoking and nonsmoking status, and had reasonably high citation impacts (i.e., ≥ 10 citations, while also factoring in the recency of publication). Approximately 70 between-subjects studies met our inclusionary criteria; and the studies included both cross-sectional and longitudinal designs.

We found a much smaller number of articles (< 80) addressing the questions of whether stress and NA cue smoking and whether smoking and nicotine relieve stress and NA. We included studies that incorporated the following methodological features: (a) inclusion of both pre- and postsmoking measures of affective response and either (b) between-subjects designs using nonsmokers or minimally deprived smokers (< 2 hr; e.g., Kassel & Shiffman, 1997) as comparison groups—so that we could more truly assess the effects of smoking on affect independently of withdrawal onset (see Hughes, 1991)—or (c) within-subject approaches in which subjects served as their own controls (in which one of the conditions was short-term deprivation). Finally, a similar set of selection criteria was applied to animal studies.

Between-Subjects Versus Within-Subject Processes Underlying Smoking–Affect Relationships

It is important to note that some of the processes governing smoking–affect associations are inherently between-subjects, whereas others are within-subject. For example, the question of whether smokers experience heightened NA relative to nonsmokers necessarily calls for a between-subjects level of analysis because groups of people are being compared. On the other hand, ascertaining whether stress and NA actually cues smoking requires a within-subject level of analysis, as it must be demonstrated that a given smoker smokes on occasions defined by stress or NA. Finally, some questions combine both levels of analysis. For example, the popular notion that some smokers smoke to alleviate unpleasant affect suggests that certain between-subjects variables are involved in within-subject attempts to regulate NA when it occurs. We believe these distinctions have been largely overlooked in previous analyses of smoking–affect relationships. As shown in

Table 1, the three primary questions addressed by our review may actually call for different levels of analysis, subject samples, and methodological strategies. Therefore, a guiding heuristic for our review is the differentiation of between-subjects and within-subject approaches to smoking–affect associations. Conceptual and methodological implications of such between- and within-subjects distinctions are emphasized throughout the article.

Smoking Stages

We also believe it critical that an examination of relationships between smoking and stress and NA take into account individuals' stage on the developmental continuum of smoking behavior. Smokers have been shown to proceed through a relatively well-defined developmental sequence of smoking behavior (e.g., Flay, 1993; Flay, Hu, & Richardson, 1998; Hirschman, Leventhal, & Glynn, 1984; Mayhew, Flay, & Mott, 2000; M. A. H. Russell, 1971). Furthermore, factors governing smoking behavior appear to vary across developmental smoking stage (Flay et al., 1998; Hirschman et al., 1984). Finally, recent research suggests that behavioral responsiveness to nicotine may change from adolescence to adulthood (Faraday, Elliott, & Grunberg, 2001). It is likely, then, that stress, NA, and smoking may influence one another in different ways at different stages of smoking. Thus, we examine smoking–affect relationships across the stages of smoking initiation, maintenance, and relapse. Moreover, we believe that information gleaned about smoking–affect relationships in the maintenance and relapse stages may help shed light on these associations among smoking initiates.

Drawing on Flay's (1993) stage model of smoking, we define the *initiation* stage herein as including both initial trying, which covers the first two or three cigarettes, and experimentation, which involves repeated but irregular use over an extended period of time. The *maintenance* stage includes patterns of regular use (ranging from weekend to daily smoking), and nicotine dependence, which reflects the development of a chronic, daily pattern of nicotine use. Finally, the *relapse* stage refers to resumption of smoking after a period of tobacco abstinence.

Other Issues

Although our primary interest lies in the relationship between smoking and stress and negative mood, we incorporate data on the effects of nicotine, as it is believed to be the primary psychoactive constituent in tobacco smoke (Benowitz, 1999; USDHHS, 1988). Thus, in concert with our attempt to bridge gaps across different disciplines, we also draw from the animal literature wherever possible in order to further elucidate the link between smoking and stress and NA.

We then consider several potential mechanisms underlying nicotine–stress–NA associations. We describe models that attempt to explain how smoking and/or nicotine may reduce affective distress, as well as those that propose explanations for smoking–NA associations even in the absence of any true NA alleviation from smoking (e.g., cueing). The applicability of potential mechanisms to the three developmental stages of smoking are also considered. We conclude the article with recommenda-

tions for future strategic research initiatives derived from a transdisciplinary¹ perspective.

In sum, the conceptual and organizing framework for our review takes the form of an incomplete factorial design, wherein stage of smoking is crossed with between- and within-subjects questions regarding the relations among stress and NA variables and nicotine and smoking variables. The same strategy is applied to animal studies, from which nicotine effects can be more clearly discriminated from behavioral and non-nicotine aspects of smoking. Such an approach allows for consideration of linear and nonlinear, as well as direct and indirect, relations among these variables. Moreover, it allows for in-depth consideration of mechanisms underlying any observed between- and within-subjects associations. Indeed, as we emphasize throughout the article, mechanisms and causal processes underlying comorbidity (e.g., smokers are more depressed than nonsmokers) ultimately can only be tested through within-subject approaches (Swendsen & Merikangas, 2000). Finally, integral to our organizational framework is an emphasis on context (Kassel, 2000b).

What Is Meant by Stress and NA?

Because an in-depth discussion of stress and NA is beyond the scope of this article, we consider brief, working definitions of these complex constructs.

Stress

Definitions of the term *stress* have varied across disciplines, theoretical orientations, and levels of analysis, with examples ranging from (a) events or experiences that are normatively or objectively associated with large adaptive demands (e.g., death, divorce); (b) individuals' subjective appraisal of their abilities to cope effectively with external demands (e.g., Carver, Scheier, & Weintraub, 1989; Lazarus & Folkman, 1984); and (c) the responses of specific physiological systems to homeostatic challenge, whether of a psychological or physical nature (Cannon, 1932; Selye, 1952). In reviewing published work reflecting these varied perspectives, we have chosen integrative definitions of both stressors and the stress response. *Stressors* are defined very broadly as situations in which environmental demands tax the adaptive capacity of an organism. The *stress response* is defined as the cognitive, emotional, and physiological changes that follow a stressor (Chrousos & Gold, 1992; Cohen, Kessler, & Gordon, 1995).

Emotional reactions to stress typically involve changes in the type or intensity of mood, be it negative or positive, and such responses are most often measured by self-report (Stone, 1995). Peripheral physiological responses to stress are typically described as involving two main systems: the hypothalamic–pituitary–adrenocortical (HPA) axis and the sympathetic axis. Activation of the HPA axis results in a cascade of neural events—corticotropin-releasing factor (CRF) is released from the hypothalamus, leading to the release of adrenocorticotropin hormone from the pituitary—eventuating in the release of glucocorticoids (principally cortisol in humans and corticosterone in animals) from the adrenal cortex. Once released, glucocorticoids affect numerous target tissues and physiological processes, as well as neuroendocrine structure and functioning (McEwen, 1998; McEwen & Stellar, 1993; Sapolsky,

Romero, & Munck, 2000). Activation of the sympathetic axis triggers the release of epinephrine and norepinephrine (NE) from the adrenal medulla. These hormones then bind to receptors throughout the body, producing physiological signs of arousal including increases in blood pressure and heart rate.

Although often neglected in studies of stress and smoking, several neurochemicals, including CRF, NE, and neuropeptide Y (NPY), are also important components of the stress response. CRF, in addition to its role as a releasing factor in the HPA axis cascade, is believed to function as a primary neurotransmitter mediating the autonomic and behavioral responses to stress (Dunn & Berridge, 1990; Owens & Nemeroff, 1991). NE and the locus coeruleus also have a role in the stress response (Bremner, Krystal, Southwick, & Charney, 1996), with increases in firing of locus coeruleus neurons and NE release following acute and chronic stress exposure (Levine, Litto, & Jacobs, 1990; Nisenbaum & Abercrombie, 1992; Pavcovich, Cancela, Volosin, Molina, & Ramirez, 1990). NPY's effects, on the other hand, appear to be anxiolytic (Heilig & Murison, 1987; Heilig, Soderpalm, Engel, & Widerlov, 1989), with disruptions of NPY receptor production leading to increases in behavioral signs of anxiety (Wahlestedt, Pich, Koob, Yee, & Heilig, 1993) but overexpression of NPY receptors resulting in reductions in anxiogenic behaviors (Thorsell et al., 2000).

NA

NA has been defined by Watson, Clark, and Tellegen (1988) as a “general dimension of subjective distress and unpleasurable engagement that subsumes a variety of aversive mood states, including anger, contempt, disgust, guilt, fear, and nervousness, with low NA being a state of calmness and serenity” (p. 1063). The construct of NA, then, is rooted in the notion of nonspecificity, of not differentiating among various types of negatively valenced emotional states. It should be acknowledged up front, however, that considerable debate still persists as to precisely what affect and emotion are and how they are best measured (Niedenthal, Halberstadt, & Innes-Ker, 1999).²

Most would agree that a one-dimensional model consisting of a valence (e.g., pleasant–unpleasant) dimension is not comprehensive enough to capture the full realm of emotions. Implicit in such a unidimensional account is the notion that NA reduction and positive affect enhancement are actually the same phenomenon. A more complete model of emotional response is a two-factor model which, in addition to valence, includes an arousal dimension as well (e.g., Lang, Bradley, & Cuthbert, 1990; J. A. Russell, 1989; see also Schachter & Singer, 1962). According to this conceptu-

¹ To be clear, a transdisciplinary approach differs from both interdisciplinary and multidisciplinary biopsychosocial approaches in the following way. Whereas the latter two emphasize different disciplines working on a shared topic area from their own, unique disciplinary perspectives, transdisciplinary research involves a process by which researchers from different disciplines work together “using a shared conceptual framework that draws together discipline-specific theories, concepts and approaches to address a common problem” (Turkkan, Kaufman, & Rimer, 2000, p. 11).

² Throughout this article, we use the terms *affect* and *emotion* to denote the same construct, both essentially reflecting relatively brief feelings that are most often attributable to a known precipitant. *Subjective distress*, *affective distress*, and *negative affect* are also used interchangeably.

alization, the emotion “fear” would be high on the arousal dimension and low (unpleasant) on the valence dimension. “Relaxed” would be represented low on the arousal and high on the valence dimension. Other two-dimensional models of affect (e.g., negative and positive affect) have also proven influential in shaping the field’s thinking about emotion and how it is best conceptualized and measured (e.g., Watson & Tellegen, 1985; Watson, Wiese, Vaidya, & Tellegen, 1999).

A second major class of theories of emotions proposes that emotional states are not meaningfully reducible to a smaller set of common dimensions. The basic emotions view posits that emotional states (e.g., happiness, sadness, anger, disgust, and fear) have different biological determinants derived through evolutionary adaptation (e.g., Ekman, 1984; Johnson-Laird & Oatley, 1992; Tomkins, 1963, 1991, 1992). The discrete emotions approach (e.g., Izard, 1993), on the other hand, though acknowledging a neural base for emotional experience, emphasizes the role played by cultural influences and personal experiences in developing and defining emotions.

It is important to keep these different conceptualizations of stress and emotion in mind, particularly within the context of how smoking and nicotine researchers generally assess these constructs. Depending on one’s theoretical orientation to the study of emotion, different questions might be posed with respect to the relationship between affect and smoking. Similarly, interpretation of findings may vary as a function of one’s working model of stress and emotions.

ROLE OF STRESS AND NA ACROSS THE STAGES OF SMOKING

We now selectively review the literature on the relationships among smoking, nicotine, stress, and NA. Because we believe that motives for smoking, as well as acute nicotine effects, may vary over the developmental course of smoking, we address these issues across three smoking stages. Table 2 presents an overview of the findings across all smoking stages.

Smoking Initiation and Experimentation

Predisposing Characteristics

It has been proposed that variability in smoking status, as well as acute responses to nicotine, may be attributable to stable char-

acteristics of smokers (Gilbert & Gilbert, 1995; O. F. Pomerleau, 1995). For example, numerous studies have found that smoking is positively associated with personality dimensions characterized by affective distress, such as neuroticism (e.g., McCrae, Costa, & Bosse, 1978) and psychoticism (Spielberger & Jacobs, 1982). Moreover, several longitudinal studies have demonstrated that adolescents who are more neurotic or extraverted are also at heightened risk to begin smoking (Cherry & Kiernan, 1976; Sieber & Angst, 1990). This is important to note, as these personality traits are believed to have a high degree of heritability (Zuckerman, 1991).

There is also evidence suggesting that many psychiatric disorders may be familial and that genetic factors account for a significant proportion of the variance in their etiology (Merikangas, 1995). Just as certain genetically transmitted personality traits (e.g., neuroticism, extraversion, psychoticism) are linked to smoking onset and dependence, so too are several major forms of psychopathology (Breslau, 1995), including depression, schizophrenia, and conduct disorder. Moreover, recent work at the receptor level reveals that neuroticism is associated with NA-motivated smoking among smokers with the short allele genotype of the functional polymorphism 5-HTTLPR of the serotonin transporter gene (Lerman et al., 2000) and that depressed smokers homozygous for the short allele of the dopamine (DA) DRD4 gene were more likely to attribute their smoking to NA reduction relative to those heterozygous or homozygous for the long DRD4 alleles (Lerman et al., 1998).

Another manner in which innate constitutional differences might affect the smoking–affect relationship is through initial sensitivity to nicotine. There is reason to believe that early exposure to nicotine in individuals with high innate sensitivity may produce not only aversive effects but also reinforcing consequences, including improvement in affect (O. F. Pomerleau & Pomerleau, 1984). Several findings implicate the potentially important role of responsivity to smoking—including emotional reactivity—early in the smoker’s career (Eissenberg & Balster, 2000; O. F. Pomerleau, Collins, Shiffman, & Pomerleau, 1993; O. F. Pomerleau, Pomerleau, & Namenek, 1998).

Studies of both rats and mice also support the hypothesis that differences in sensitivity to nicotine effects may be genetically related (Acri, Brown, Saah, & Grunberg, 1995; Marks, Stitzel, & Collins, 1989). Correspondingly, some strains of rats and mice self-administer more nicotine than other strains, although this may

Table 2
Overview of Findings of Primary Research Questions Across Smoking Stages

Smoking stage	Do stress and negative affect (NA) promote smoking?		
	Do smokers & nonsmokers differ on levels of stress & NA?	Do stress & NA cue smoking?	Does smoking reduce stress & NA?
Initiation	Cross-sectional studies suggest <i>yes</i> , particularly for externalizing symptoms and, to a lesser extent, depressive symptoms; anxiety is less clear	Unknown, other than self-report data (longitudinal studies show inconsistent findings regarding NA’s ability to predict smoking onset)	Unknown, other than self-report data
Maintenance	<i>Yes</i> ; high levels of comorbidity	Unclear; laboratory studies and self-report data offer a tentative <i>yes</i>	Sometimes; mixed findings
Relapse	Not applicable	<i>Yes</i> ; both self-report and real-time data	Few data; trend toward smoking worsening or having no effect on affect

just reflect a general susceptibility to self-administer drug, as the same strain differences are apparent in the self-administration of other drugs as well (Robinson, Grun, Pauly, & Collins, 1996; Shoaib, Schindler, & Goldberg, 1997).

In sum, individual differences in personality (Heath, Madden, Slutske, & Martin, 1995), innate sensitivity to nicotine (O. F. Pomerleau, 1995), and psychopathology (Gilbert & Gilbert, 1995) are among some of the likely variables associated with NA that appear to predispose to smoking. Both animal and human studies also support the view that genetic differences contribute to the propensity to self-administer nicotine. Such results derive from between-subjects levels of analysis and thus point to possible etiological (within-subject) mechanisms governing smoking-affect associations. However, these results cannot be construed as validating within-subject mechanisms.

Initiation: Do Stress and NA Promote Smoking?

The pathways to becoming a smoker are complex and likely involve more than just genetic makeup. In fact, social factors, such as peer affiliations and peer socialization (e.g., Oetting & Donnermeyer, 1998), have emerged in the literature as perhaps the most potent and reliable predictors of smoking initiation and experimentation. There is also reason to believe that adolescents who experience affective distress are at heightened risk to take up smoking and progress to nicotine dependence. For example, among the many adolescents who try cigarettes, those who continue on to become regular smokers are more likely to be stressed or experience NA (Chassin, Presson, Sherman, Corty, & Olshavsky, 1984; Stein, Newcomb, & Bentler, 1996). It is thus critical to distinguish the processes that govern smoking initiation and experimentation from those that underlie progression to nicotine dependence (Colby, Tiffany, Shiffman, & Niaura, 2000; Kassel, 2000a; Shadel, Shiffman, Niaura, Nichter, & Abrams, 2000).

Stress

Numerous studies have found associations between various indices of psychological stress and smoking uptake. Childhood abuse and household dysfunction (Felitti et al., 1998), adverse childhood experiences (Anda et al., 1999), parental divorce (Patton et al., 1998a), negative life events (Koval & Pederson, 1999; Siqueira, Diab, Bodian, & Rolnitzky, 2000), acute and chronic stressors (Koval, Pederson, Mills, McGrady, & Carvajal, 2000), and perceived stress (Dugan, Lloyd, & Lucas, 1999; Siqueira et al., 2000) all have been found to increase the risk for smoking uptake. Byrne and Mazanov (1999) reported that the impact of different types of stressors on smoking uptake varied by gender such that relationships were generally stronger for girls, particularly with respect to family-related stress and smoking. Finally, affective distress and negative life events also appear to predict transition from experimental to regular smoking (see Hirschman et al., 1984; Koval et al., 2000; Orlando, Ellickson, & Jinnett, 2001; Siqueira et al., 2000).

In sum, there is fairly strong evidence that adolescents who experience stress (assessed in a variety of ways) are at heightened risk to begin smoking, as well as to progress to more regular smoking. Although convergent results from both cross-sectional and prospective studies suggest that stress is often an antecedent to

smoking onset and not simply a consequence of smoking initiation (e.g., Gorsuch & Butler, 1976; Kandel, Kessler, & Margulies, 1978), potential third-factor causal confounds render interpretation of some studies difficult.

NA

Numerous cross-sectional studies have suggested an association between smoking initiation and various manifestations of NA, most notably depression (Covey & Tam, 1990; Gritz et al., 1998; Kendler et al., 1993; Patten, Choi, Vickers, & Pierce, 2001; Patton et al., 1996; Pederson, Koval, McGrady, & Tyas, 1998) and, to a lesser extent, anxiety (Patton et al., 1996) and neuroticism (Cherry & Kiernan, 1976).

Depression. A number of large-scale longitudinal studies have yielded data showing that depressive symptoms in particular are linked to, and precede the onset of, smoking initiation and experimentation (Brook, Cohen, & Brook, 1998; Brown, Lewinsohn, Seeley, & Wagner, 1996; Escobedo, Reddy, & Giovino, 1998; Ferdinand, Blum, & Verhulst, 2001; Kandel, Davies, Karus, & Yamaguchi, 1986). At the same time, several recent investigations have either (a) been unable to demonstrate a prospective link between depression and smoking uptake (Dierker, Avenevoli, Merikangas, Falherty, & Stolar, 2001; Goodman & Capitman, 2000; Wang et al., 1998; White, Pandina, & Chen, 2002), (b) found differential effects for boys and girls (depression predicts smoking uptake for girls but not for boys; Costello, Erkanli, Federman, & Angold, 1999; or depression predicts initiation for boys but not girls; Killen et al., 1997), or (c) reported that ethnicity moderates the association between depression and smoking initiation (depression predicts smoking uptake among Caucasians and Hispanics but not among African Americans; Gritz et al., 1998).

Although it is difficult to reconcile such differential findings, some of the variance is likely attributable to utilization of different time frames, dissimilar cultural contexts, different depression measures, univariate versus multivariate analytic procedures, and varying definitions of smoking behavior (e.g., any smoking vs. daily smoking). Indeed, a close perusal of the data suggests that whereas depression may be a potent predictor of heavy smoking and nicotine dependence among adolescents and young adults (e.g., Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Dierker et al., 2001; Fergusson, Lynskey, & Horwood, 1996; Kandel & Davies, 1986), it is less consistently successful at differentiating nonsmokers from smoking initiators and experimenters (Dierker et al., 2001; Stein et al., 1996; Wang et al., 1998). Results from Patton et al. (1998b) also suggest a mediational mechanism whereby depressive and anxiety symptoms appear to be associated with higher risk for smoking initiation through an increased susceptibility to peer smoking influences. Killen et al. (1997) similarly found that, for boys only, those who had both more friends who smoked and higher depressive scores were more likely to have initiated smoking over a 3-year follow-up period. Thus, moderator and mediator approaches hold potential in delineating smoking-affect relations among adolescents and are in need of further study.

Finally, several longitudinal reports suggest that the relationship between smoking and depression is reciprocal such that smoking also predicts the subsequent development of depressive symptoms (e.g., Brown et al., 1996; Choi, Patten, Gillin, Kaplan, & Pierce,

1997; Goodman & Capitman, 2000; Windle & Windle, 2001; Wu & Anthony, 1999). Thus, some of the covariance in smoking status and depressive symptomatology may be attributable to the fact that smoking predisposes to the development of depression.

Anxiety. Of the few studies that have examined the role of anxiety in the onset of smoking, the findings have been mixed. Cross-sectional research has indicated that adolescents with symptoms of anxiety are at higher risk for smoking initiation than asymptomatic adolescents (Patton et al., 1996) and that adolescents and young adults with social fears have an increased risk of onset of nicotine dependence (Sonntag, Wittchen, Hofler, Kessler, & Stein, 2000).

Longitudinal studies, however, have yielded more equivocal findings. Indeed, a number of well-designed prospective investigations have found that anxiety disorders do not reliably predict the onset of cigarette smoking during adolescence (Costello et al., 1999; Dierker et al., 2001; Johnson et al., 2000; McGee, Williams, & Stanton, 1998; Patton et al., 1998b) or adulthood (Johnson et al., 2000). Moreover, at least one study (Costello et al., 1999) has suggested that anxiety disorders may actually be prophylactic, at least in the sense that they delay the onset of smoking among adolescents. However, whereas the relationship between anxiety disorders and smoking onset appears tenuous, the relationship between anxiety and nicotine dependence (even among teenagers) appears robust (Dierker et al., 2001; Johnson et al., 2000). Thus, once again, the importance of differentiating among levels of cigarette use becomes clear (Hughes, 2001; Kassel, 2000a). Findings from Dierker et al. (2001) lend further support to this point. They found that, whereas anxiety disorders distinguished neither smoking experimenters from nonsmokers nor regular smokers from light smokers, anxiety did significantly differentiate light smokers from nicotine-dependent smokers. Finally, as was observed in the relationship between smoking and depressive symptomatology, emerging evidence similarly suggests that smoking in adolescence predicts the subsequent development of anxiety disorders (Johnson et al., 2000) and emotional distress (Orlando et al., 2001).

Externalizing Behaviors

Cross-sectional and longitudinal associations between externalizing symptoms such as conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity disorder and smoking onset in adolescence have proven robust (Kandel et al., 1997; Kellam & Anthony, 1998; Lynskey & Fergusson, 1995; McMahon, 1999; Miller-Johnson, Lochman, Coie, Terry, & Human, 1998). Externalizing disorders appear to also discriminate light from heavy and dependent smoking (Adalbjarnardottir & Rafnsson, 2002; Cornelius, Lynch, Martin, Cornelius, & Clark, 2001). Of course, because externalizing problem behaviors often correlate highly with affective disorders (Lambert, Wahler, Andrade, & Bickman, 2001; McMahon, 1999; Ryan, 2001), the observed association between smoking initiation and externalizing behaviors may be attributable to NA rather than to disruptive behavior per se. However, at odds with such an interpretation is the fact that the observed associations between externalizing behavior and ever-smoking have proven reliably stronger, even when controlling for other psychiatric disorders, than have the associations between affective disorders and smoking onset (Breslau, 1995; Ferdinand,

Blum, & Verhulst, 2001; Milberger, Biederman, Faraone, Chen, & Jones, 1997; Miller-Johnson et al., 1998; Whalen, Jamner, Henker, & Delfino, 2001). Indeed, these observations suggest an alternative interpretation of the findings linking NA and smoking onset such that the relationship may actually be spurious, attributable to externalizing symptoms as a third variable. This hypothesis clearly warrants further empirical scrutiny.

Whereas the mechanisms underlying the association between smoking onset and externalizing behaviors are not well understood, it is possible that problems in underregulation of behavior and emotion play a role in the development of smoking behavior. Several personality traits (e.g., disinhibition, risk taking) associated with both conduct problems and deficits in self-regulation appear to heighten the risk of smoking onset (e.g., Brook, White-man, Czeisler, Shapiro, & Cohen, 1997; Burt, Dinh, Peterson, & Sarason, 2000; White et al., 2002). It is interesting to note that studies from the field of alcohol use reveal that those who are at high risk for alcohol problems because of externalizing and self-regulation problems such as impulsivity and disinhibition (Sher & Levenson, 1982), antisociality (Sher, Bylund, Walitzer, Hartmann, & Ray-Prenger, 1994), and hostility (Zeichner, Giancola, & Allen, 1995) actually derive greater stress-response-dampening effects of alcohol. Kassel, Jackson, and Unrod (2000) found that college students whose expectations to successfully cope with stress and NA were low (i.e., low in emotional regulation) were at heightened risk to develop alcohol problems, even when the authors statistically controlled for coping style, drinking motives, and depression and anxiety symptoms. Taken together, these findings suggest that deficiencies in behavioral regulation and self-control—problems that underlie both externalizing and internalizing disorders—may play a role in both problematic alcohol use and smoking onset. Indeed, the high rates of comorbid use of alcohol and cigarettes among adolescents (USDHHS, 1994), coupled with evidence that a previous alcohol use disorder or nicotine dependence diagnosis increases the likelihood of subsequently being diagnosed with the other disorder (Sher, Gotham, Erickson, & Wood, 1996), suggest that the search for mechanisms underlying the concurrent use of alcohol and cigarettes is an important one that may inform both fields (Shiffman & Balabanis, 1995).

Summary

Most cross-sectional studies report a positive association between smoking onset and NA. This association appears particularly strong for depressive symptomatology; however, links between depression and smoking may be bidirectional such that smoking also increases risk for subsequent development of depression. Moreover, recent evidence suggests that cigarette smoking may also increase the risk of agoraphobia, generalized anxiety disorder, and panic disorder during late adolescence and early adulthood (Johnson et al., 2000). Whereas the most popular interpretation of the smoking–NA link is that it reflects self-medication processes, it is important to reiterate that such comorbidity ultimately says nothing about within-subject processes inherent to the self-medication model. This is especially true given findings suggestive of reverse causality (i.e., over time, smoking may lead to increased NA).

At the same time, longitudinal studies have yielded a more mixed picture regarding the role of depression, and particularly

anxiety, in the onset of smoking: Whereas a number of studies report that depressive and anxiety symptoms precede smoking initiation, others find no significant temporal association. Thus, the extent to which the widely held belief that depression and anxiety predate smoking initiation is true must be called into question. At the very least, it seems critical to consider the role played by potential moderators (e.g., ethnicity, gender) and mediators (e.g., peer influence) when examining prospective links between various manifestations of NA and subsequent smoking behavior.

Finally, the strong relationship between externalizing disorders and smoking initiation warrants further empirical scrutiny and theory development. Correspondingly, whether individuals who are underregulated in behavior derive greater NA reduction from smoking should be assessed.

Initiation: Does Smoking Reduce Stress and NA?

Although there is a dearth of empirical work devoted to answering this important question, several studies offer some insight into the motives associated with smoking initiation. McNeill, Jarvis, and West (1987) found that the most frequently cited motive for smoking among a sample of female adolescent smokers was that smoking is calming. Dozois, Farrow, and Miser (1995) and Nichter, Nichter, Vuckovic, Quintero, and Ritenbaugh (1997) similarly found that “smoking to relax” and “stress reduction” were commonly reported motives among adolescent smoking initiates.

Although the findings from these studies may be compelling, the conclusions that can be drawn from them are limited because of the highly subjective and retrospective nature of the data. Controlled laboratory studies would be useful to determine whether and when smoking exerts genuine stress-dampening effects. Acknowledging the ethical constraints associated with administration of nicotine to minors, such information is nonetheless crucial in order to further knowledge of the effects of nicotine in new smokers and the extent to which individual differences in emotional responsivity might be predictive of smokers’ developmental trajectory. Daily diary methods offer another method through which within-subject processes governing adolescent smoking behavior could be identified (Mermelstein, Flay, Hedeker, Crowe, & Shiffman, 2001; Whalen et al., 2001).

Animal studies can be used toward delineating within-subject smoking–affect relationships as well. Indeed, in a recent study of adolescent rats, females were more sensitive to the anxiolytic effect of nicotine than were males (Cheeta, Irvine, Tucci, Sandhu, & File, 2001). Moreover, it has also been reported that, across a range of biobehavioral responses, including anxiolysis, adolescent rats differed from their adult counterparts (Faraday et al., 2001). Thus, the use of animal studies to model adolescent nicotine–affect relationships shows great promise.

Summary

Although the extant database is small, there is compelling evidence that stress often precedes smoking initiation. A diverse array of negative life events encompassing multiple domains have been found to predict the onset of smoking. Although the precise mechanisms underlying such associations have not been well articulated, it is possible that stress affects neurophysiological, neuro-anatomical, and neurochemical changes within biological systems

that are also affected by smoking and nicotine (Gordon, 2002). Indeed, early response to stress may modify neurodevelopment in permanent ways such that these neuroadaptations occur within the same neuronal systems that comprise drug-reward circuitry (Thadani, 2002).

Whereas cross-sectional studies generally support associations between various forms of NA and smoking status, the findings have been less convincing with respect to prospective links. Indeed, although depression appears a potent predictor of nicotine dependence, it fares less well as a predictor of smoking initiation (Dierker et al., 2001). Other studies have similarly suggested that anxiety does not reliably predict smoking onset. Finally, mechanisms by which stress and NA might predispose to smoking are unknown. Moreover, the specificity of the link between smoking and affective distress must be questioned, as affective distress is associated with numerous deviant behaviors in adolescents (see, e.g., McMahon, 1994; Tubman & Windle, 1995).

Externalizing disorders emerge as the most reliable correlates and predictors of smoking initiation. Again, although such disorders are not defined in terms of negative affectivity, they frequently co-occur with disorders of affect. As such, an intriguing, although speculative, possibility is that it is disordered emotional regulation—and not NA per se—that lies at the root of links between NA and smoking behavior (see Kassel et al., 2000, for a discussion of this issue in terms of problematic alcohol use).

Whether smoking genuinely reduces subjective stress among new smokers remains unanswered. Although several studies suggest that new smokers report that smoking is relaxing, no laboratory or field studies have yet addressed this important issue. In sum, the answers to our three questions as posed to the initiation period are as follows: (a) Whereas individuals who experience heightened stress appear at greater risk to begin smoking, the findings regarding NA are less robust—a number of potentially important mediators (i.e., peer influence) and moderators (i.e., ethnicity, gender) of the NA–smoking link clearly warrant further study; (b) other than smokers’ self-report, no data bear on the question of whether stress and NA genuinely cue smoking; and (c) virtually no studies have yet ascertained whether smoking effectively reduces stress and NA (although see Corrigan, Zack, Eisenberg, Belsito, & Scher, 2001).

Smoking Maintenance

*Maintenance: Do Stress and NA Promote Smoking?*³

Stress

Most studies have used between-subjects levels of analysis to compare smokers with nonsmokers on various indices of stress

³ One could argue that it is actually impossible to analyze smoking–affect interactions at the maintenance stage independently, as the population effects of smoking status during maintenance can be attributed to initiation (for those who increase their smoking) and to cessation (for those who subsequently quit). Put simply, smokers in the maintenance stage are those who initiated and haven’t yet quit. Indeed, we believe this is a valid argument. At the same time, questions as to whether NA and stress cue smoking are pertinent, as are inquiries into the effect of affective distress on smoking rate among those in the maintenance stage.

(e.g., occupational and marital stress, negative life events, divorce, financial difficulties), with the majority finding that smokers report more stress than nonsmokers (e.g., Jorm et al., 1999; Kirkcaldy, Cooper, Brown, & Althanasou, 1994; Melamed, Kushnir, Strauss, & Vigiser, 1997; Naquin & Gilbert, 1996; Vollrath, 1998). Similar between-subjects analyses have also been used to differentiate stress levels among types of smokers on the basis of amount smoked. For example, Billings and Moos (1983) found that, although higher levels of environmental stressors differentiated light from heavy smokers, they did not distinguish smokers from nonsmokers. Whereas Kassel, Shiffman, Gnys, Paty, and Zettler-Segal (1994) and Vollrath (1998) did not detect differences in perceived stress levels between light and heavy smokers, a number of other studies that used more objective indices of stress found that amount smoked generally covaried with stress, negative life events, and NA (Conway, Vickers, Ward, & Rahe, 1981; Hellerstedt & Jeffrey, 1997; Ogden & Mitandabari, 1997; Steptoe, Wardle, Pollard, Canaan, & Davies, 1996). It should be noted that the methodologies used by these various studies vary considerably, from those using daily diary methods (Conway et al., 1981) to those using large epidemiological surveys (Hellerstedt & Jeffrey, 1997). Nonetheless, the fact that the findings generally converge on the basis of whether studies used within- or between-subjects designs actually lends greater support to the observed associations. Finally, moderators of the relationship between stress and smoking have also been explored and include race (Biafora, Warheit, Vega, & Gil, 1994) and history of sexual abuse (Hourani, Yuan, Bray, & Vincus, 1999).

An interesting naturalistic study revealed that, in spite of dramatic increases in the cost of cigarettes and the need to use scarce cash for essential goods for self and family, there were significant elevations in smoking among health workers in Sarajevo, Bosnia, during wartime (Creson, Schmitz, & Arnoutovic, 1996). The authors interpreted these results within a smoking-to-cope framework because the health care workers attributed their increased smoking to stress-related causes. In another naturalistic study (Dejin-Karlsson et al., 1996), it was found that, relative to pregnant women who quit smoking, women who continued to smoke during their pregnancy were unmarried, had little social support, and reported more job strain.

Given these aggregate findings, there is reason to believe that both smoking status (smokers vs. nonsmokers) and amount smoked covary with various indices of stress. In an effort to establish the direction of causality, several laboratory studies have demonstrated that during stressful situations, smoking intensity increases (Cherek, 1985; Mangan & Golding, 1984; C. S. Pomerleau & Pomerleau, 1987), smokers tend to smoke more (Epstein & Collins, 1977; Rose, Ananda, & Jarvik, 1983; Schachter, Silverstein, & Perlick, 1977), and self-reported desire to smoke is heightened (Perkins & Grobe, 1992). Taken together, these within-subject studies make a compelling case that stress increases—that is, cues—smoking among regular smokers.

Animal Studies of Stress

The relationship between stress and drug intake has received recent attention in animal models of drug abuse, and there is an emerging literature on the effects of stress on drug self-administration in animals. The acquisition and reinstatement of

cocaine or heroin self-administration in rats can be increased by exposure to stressors such as footshock or injections of corticosterone, and these effects are blocked by glucocorticoid receptor antagonists, suggesting involvement of the HPA axis in psychomotor stimulant self-administration (Goeders & Guerin, 1994; Mantsch, Saphier, & Goeders, 1998; Shaham, Erb, Leung, Buczek, & Stewart, 1998). At least one study (Buczek, Le, Wong, Stewart, & Shaham, 1999) has examined the role of stress on nicotine self-administration in animals, reporting that footshock stress reinstates nicotine- but not sucrose-seeking behavior.

The effects of footshock stress on nicotine-seeking behavior are not unique. Similar results have been reported for reinstatement of alcohol, heroin, and cocaine self-administration (Ahmed & Koob, 1997; Lê et al., 1998; Shaham, Erb, & Stewart, 2000). Likewise, food deprivation has been shown to increase self-administration of nicotine as well as of *d*-amphetamine and cocaine (de la Garza & Johanson, 1987). Thus, this general increase in drug-seeking behavior elicited by different stressors makes it difficult to ascribe unique stress-cueing effects to nicotine.⁴

NA

A large portion of the literature appears to support the association between smoking status and multiple indices of NA. Numerous between-subjects studies point to positive associations between smoking status and neuroticism (e.g., Kandel & Davies, 1986; Sieber & Angst, 1990), hostility and anger (e.g., Pritchard & Kay, 1993; Seltzer & Oechsli, 1985), dysphoria (e.g., Anda et al., 1990; Covey & Tam, 1990), and anxiety (e.g., Schneider & Houston, 1970; Williams, Hudson, & Redd, 1982). Although many of these studies primarily assessed subsyndromal symptoms, there is evidence pointing to strong associations between smoking and diagnosable clinical syndromes marked by persistent NA.

Depression. As noted with regard to smoking initiation, depressive symptomatology, in particular, emerges as a strong correlate of smoking status (see Breslau, 1995). In 1978, Waal-Manning and de Hamel reported that smokers had elevated depressive symptoms relative to nonsmokers. Similar relationships have been found in studies using large nationally representative samples (e.g., Anda et al., 1990; Degenhardt & Hall, 2001). In a study of 3,000 young adults, Breslau, Kilbey, and Andreski (1991) found that those who met criteria for nicotine dependence were also more likely to meet criteria for major depression. Breslau, Kilbey, and Andreski (1993) also reported that a history of major depressive disorder produced a two-fold increased risk for progression to nicotine dependence. Findings from Breslau, Kilbey, and Andreski (1994) indicated that the association between major depression and smoking was specific to nicotine dependence; nondependent smokers did not differ from nonsmokers in this

⁴ As noted earlier, it is clear that a host of psychotropic drugs other than nicotine are often used to diminish NA. It is also likely that a variety of nonpharmacological influences also yield similar outcomes (e.g., stress reduction). Thus, nonconsummatory behaviors as diverse as gambling, exercise, sky diving, and sex are thought to produce pleasure and reduce NA (at least for some individuals). Correspondingly, it is conceivable that administration of any reinforcer may be more likely following stress and NA.

respect. As was observed in the initiation stage, the presence of nicotine dependence also appears to heighten the risk for subsequent development of major depression (Breslau et al., 1993). In our view, the best studies suggest that the frequently observed link between nicotine dependence and depression may reflect (a) bidirectional causal processes (e.g., smoking to alleviate depressed mood and neuropharmacological effects of nicotine on neural substrates linked to depression) and (b) common factors (e.g., neuroticism) that predispose to both disorders (Breslau et al., 1993, 1998; Kendler et al., 1993).

Anxiety. A number of studies also point to a fairly strong relationship between anxiety and smoking status (e.g., Degenhardt & Hall, 2001; Pohl, Yeragani, Balon, Lycaki, & McBride, 1992), although this association has not received as much attention as the link between smoking and depression. Breslau et al. (1991, 1994) found significant correlations between mild nicotine dependence and any anxiety disorder. Moreover, persons who met criteria for nicotine dependence had significantly higher rates of anxiety disorders relative to nonsmokers and nondependent smokers. Comparison of nicotine-dependent individuals to a combination of both nondependent smokers and nonsmokers revealed significantly greater odds ratios for obsessive compulsive disorder and phobias for both male and female dependent smokers (Breslau et al., 1994). Again, however, given that these data all come from correlational studies, the extent to which smoking may actually precede, or even cause, elevations in anxiety cannot be ruled out. Finally, one study with a sample of medical patients reported that whereas anxiety symptoms were significantly higher among smokers than nonsmokers, when controlling for depressive symptomatology, the association between anxiety and current smoking disappeared (Kick & Cooley, 1997). Given the high degree of covariance between depression and anxiety symptoms, such findings strongly support the use of multivariate approaches to the problem of delineating smoking-affect relationships.

Summary

Although there are a small number of negative findings, the majority of evidence supports the notion that stress and NA are strongly linked to smoking at the between-subjects level of analysis; smokers report more stress and NA relative to nonsmokers. Moreover, there appears to be a dose-response relationship, or threshold effect, as affective distress is associated more with heavy smoking and nicotine dependence and less so with intermittent or nondependent smoking (e.g., Breslau et al., 1994).

The answer to the within-subject question of whether stress and NA act as cues for smoking is less clear. Laboratory studies have shown that NA usually increases smoking behavior;⁵ however, one must remember that just because stress and NA can cue smoking in the lab does not necessarily mean that they cue smoking in the real world. Indeed, the only field studies of which we are aware that used real-time self-monitoring reported inconsistent findings. Shiffman et al. (2002) found that NA had virtually no association with cueing smoking, whereas Delfino, Jamner, and Whalen (2001) found that anxiety and decreased alertness predicted subsequent smoking in men only.

Maintenance: Does Smoking Reduce Stress and NA?

Stress and Anxiety

Given the ubiquitous assertions that smoking alleviates tension, relatively little research has actually examined this issue. Using various forms of anticipatory anxiety (most of which have taken the form of cognitive challenge), several studies found that smoking significantly reduced self-reported anxiety relative to not smoking (e.g., Jarvik, Caskey, Rose, Herkovic, & Sadeghpour, 1989; Perkins, Grobe, Fonte, & Breus, 1992; C. S. Pomerleau & Pomerleau, 1987; O. F. Pomerleau, Turk, & Fertig, 1984). However, there is also reason to believe that nicotine effects may be moderated by contextual factors. Kassel and colleagues (Kassel & Shiffman, 1997; Kassel & Unrod, 2000) have reported that smoking reduces anxiety under controlled laboratory conditions, but only in the presence of benign distraction. In all of these investigations, it is unlikely that group differences were attributable to withdrawal effects because subjects who did not smoke were minimally deprived (in most instances, less than 1.5 hr).

A few studies have found that smoking lessens subjective stress not only in anticipation of a stressor but in the direct presence of a stressor as well. These stressors have included aversive noise bursts (Woodson, Buzzi, Nil, & Battig, 1986), annoying aircraft noise (Perlick, 1977), viewing a stressful film (Gilbert, Robinson, Chamberlin, & Spielberger, 1989), and participation in stressful social interactions (Gilbert & Spielberger, 1987).

In a series of naturalistic, self-monitoring studies, Parrott (1995) found that self-reported feelings of stress and anxiety were significantly lower postsmoking than presmoking among a sample of smokers who completed a brief questionnaire before and after each cigarette. However, relative to a nonsmoking control group, the postsmoking stress levels of the smokers approximated the baseline stress levels of the nonsmokers, thus suggesting that "smokers gain little real advantage from cigarettes, but smoke mainly to forestall nicotine depletion" (Parrott, 1995, p. 233). Although such an interpretation of the findings may be correct, evidence suggests that smokers are fundamentally different than nonsmokers in terms of baseline levels of stress, NA, and psychopathology (see Gilbert & Gilbert, 1995), thus calling into question the adequacy of using nonsmokers to provide a true baseline against which to compare smokers' emotional responses to nicotine. One of the only other field studies to have assessed the effect of smoking on emotion (Delfino et al., 2001) reported that smoking was followed by decreased anger levels in men and women and decreased sadness in men only. These authors made the important observation that there is not necessarily an isomorphism between the emotion that triggers smoking and the emotion that may be changed by it.

In marked contrast to all of the studies described above, however, are those that have been unable to demonstrate smoking-related differences in stress-induced NA. For instance, Hatch, Bierner, and Fisher (1983) assessed self-reported anxiety both

⁵ It is important to observe that smoking behavior in the lab has been variously defined as: (a) choosing to smoke or not, (b) number of cigarettes smoked, (c) puff duration, (d) puff volume, and (e) puff intensity. Moreover, it is not uncommon for laboratory studies to actually require subjects to smoke, with experimenter interest therefore lying primarily in topographical indices of smoking behavior.

during and after a stressful speech and described that smoking-deprived smokers were indistinguishable from those who smoked either low- or high-nicotine-yield cigarettes. Jarvik et al. (1989) found that smoking did not reduce anxiety associated with impending exposure to either aversive white noise or an auditory vigilance task. Furthermore, although the Jarvik et al. study did report smoking-induced anxiety reduction in anticipation of both the anagram and cold pressor task conditions, posttask anxiety ratings were not affected by smoking. Finally, Herbert, Foulds, and Fife-Schaw (2001) found that smoking had no effect on anticipatory anxiety, regardless of the presence or absence of benign distraction (cf. Kassel & Shiffman, 1997).

Animal Studies of Stress and Anxiety

Animal studies have yielded only mixed support for the hypothesis that nicotine has anxiolytic effects. Historically, conflict procedures have proven effective in predicting clinical anxiolytic actions of drugs, especially benzodiazepines such as diazepam (Valium) and alprazolam (Xanax). Conflict procedures involve the suppression of an ongoing rewarded behavior through the presentation of a noxious stimulus, and drugs with anxiolytic actions attenuate the suppression produced by the stimulus (Geller & Seifter, 1960; Sepinwall, Grodsky, & Cook, 1978). We know of only one study (Morrison, 1969) that examined the effects of nicotine in a conflict procedure, the results of which suggest that nicotine does not yield the same effects as benzodiazepines.

Ethologically based procedures, including the plus-maze, the black/white box, and fear-potentiated startle procedures (see Barrett & Vanover, 1993) have also been used to assess nicotine's effects on stress and anxiety. The plus-maze and black/white box procedures have in common the strategy of allowing an animal to choose between a preferred and a nonpreferred environment in the presence of a drug. Drugs that result in increasing amounts of time spent in the normally nonpreferred environments are then described as possessing anxiolytic properties. Several laboratories have shown that nicotine produces such effects, in some instances of the same magnitude as produced by diazepam (Brioni et al., 1994; Costall, Jones, Kelly, Naylor, & Tomkins, 1989; Costall, Kelly, Naylor, & Onaivi, 1989; Faraday, Scheufele, Rahman, & Grunberg, 1999; Onaivi & Martin, 1989). However, the effects of nicotine are often variable in these procedures (Balfour, Graham, & Vale, 1986). Moreover, in many instances in which anxiolytic-like effects of nicotine have been reported, there is also evidence that other drugs with no known anxiolytic actions in humans also produce the same effects. Similarly mixed results have been obtained in studies of nicotine effects on fear-potentiated startle, a procedure in which anxiolytics inhibit response to an acoustic stimulus (Hijzen, Houtzager, Joordens, Olivier, & Slangen, 1995; Marks et al., 1989). Overall, these studies suggest that in naive animals, the anxiolytic-like effects of nicotine are mild.

Some of the inconsistent findings from animal studies may be explained by differences in nicotine dosing. It has been shown that the effects of nicotine in rats are dose dependent, with low doses having anxiolytic effects, and high doses anxiogenic effects (File, Kenny, & Ouagazzal, 1998). Whereas anxiolytic effects of acute administration of nicotine have been reported in several experimental models of anxiety in both mice (Brioni, O'Neill, Kim, & Decker, 1993; Cao, Burkholder, Wilkins, & Collins, 1993) and rats

(Brioni et al., 1994; Vale & Green, 1986), these were restricted to a narrow dose range. The influence of context (e.g., group vs. single housing) has also emerged as a potentially important moderator of nicotine's acute and chronic effects on anxiety (Cheeta, Irvin, & File, 2001; Scheufele, Faraday, & Grunberg, 2000).

Finally, there are reports that, under some circumstances, nicotine can induce anxiogenic responses in rats. Direct injections of nicotine into the lateral septum resulted in consistent anxiogenic effects on two tests of anxiety (social interaction and elevated plus-maze test; Ouagazzal, Kenny, & File, 1999). Another study similarly demonstrated that, subsequent to injection of nicotine into the dorsal hippocampus, time spent in social interaction decreased (Kenny, Cheeta, & File, 2000). However, this effect was reversed by administration of the specific 5-hydroxytryptamine (5-HT_{1A}) receptor agonist, WAY 100635, thereby implicating 5-HT_{1A} as a mediator of the anxiogenic effects of nicotine in this brain region.

Smoking's Effect on Physiological Indices of Stress and NA

Physiologically, smoking appears to raise basal levels of stress hormones. Similar to the effects of other psychostimulants (Kreek & Koob, 1998), acute nicotine exposure, whether through smoking or intravenous nicotine infusion, appears to result in distinct increases in circulating levels of cortisol in humans and corticosterone in animals (Caggiula et al., 1991, 1998; Gilbert, Meliska, Williams, & Jensen, 1992; Kirschbaum, Wust, & Strasburger, 1992; Meliska & Gilbert, 1991; Wilkins et al., 1982). Chronic or long-term smoking appears to result in persistent dysregulation of the HPA stress hormones, with smokers showing hypersecretion of cortisol throughout the day compared with nonsmokers (Baron, Comi, Cryns, Brinck-Johnsen, & Mercer, 1995; Cam & Basset, 1984; Frederick et al., 1998; but see Kirschbaum, Scherer, & Strasburger, 1994) that is perhaps related to repeated acute rises from smoking (Kirschbaum et al., 1994). In line with the stress-reduction hypothesis, several studies have shown that when smokers were confronted by a psychological stressor, they exhibited attenuated increases in cortisol compared with nonsmokers, even when baseline cortisol differences were controlled for statistically (Kirschbaum, Strasburger, & Langkrar, 1993; Roy, Steptoe, & Kirschbaum, 1994). Of note, however, is that these studies were mainly conducted by the same laboratory, and included small numbers of subjects, all of whom were male.

It is important to note that the acute peripheral effects of smoking and nicotine are similar to those elicited by stress. Several investigations suggest that stress and smoking are additive in their impact on blood pressure, heart rate, and cortisol output (Davis & Mathews, 1990; MacDougall, Musante, Castillo, & Acevedo, 1988; Perkins, Grobe, Fonte, & Breus, 1992; O. F. Pomerleau & Pomerleau, 1990). As such, it is somewhat surprising that smoking is experienced as relaxing given that it induces physiological changes consonant with the stress response. Indeed, as Nesbitt (1973) observed, "The physiological and psychological effects of smoking a cigarette are seemingly in contradiction to each other. When smokers smoke, their level of physiological arousal goes up, while they report themselves as calmer and more relaxed" (p. 137). This phenomenon has been referred to as *Nesbitt's paradox* (see

Gilbert, 1979; Parrott, 1998) and is critical to formulating models of smoking's effect on stress and NA.

Hence, the question remains as to whether the reports that smoking reduces subjective stress are incongruous with smoking's effects on the body's physiology. To address this issue, several laboratory studies have examined the effects of smoking in experimentally stressed (with, e.g., pain induction, cognitive challenges) smokers on both self-reported affect and various physiological measures linked to emotion. Findings have been variable, with one study reporting a negative association between change in pulse rate and emotional arousal (as assessed indirectly by pain tolerance) among stressed smokers (Nesbitt, 1973); another finding that, although smoking reliably increased heart rate, it had no effect on subjective measures of affect (Shiffman & Jarvik, 1984); and several others reporting a dissociation between smoking's effects on both subjective stress and cardiovascular arousal (Perkins, Grobe, Fonte, & Breus, 1992) and on self-monitored changes in stress and arousal during smoking in the field (Parrott, 1994, 1998). The examination of the idea that smoking may yield independent effects on subjective and physiological dimensions can perhaps be accommodated by two-factor models of emotion discussed earlier that view arousal and affective valence as orthogonal dimensions (Mackay, Cox, Burrows, & Lazzarini, 1978; Mathews, Jones, & Chamberlain, 1990; J. A. Russell, 1997).

Animal Studies of Depression

Several studies have suggested that nicotine may exhibit antidepressant effects in rats (e.g., George, Picciotto, Verrico, & Roth, 2001; George, Verrico, & Roth, 1998; Semba, Mataka, Yamada, Nankai, & Toru, 1998). For example, Tizabi et al. (1999) reported that acute and chronic administration of nicotine significantly improved the performance of Flinders Sensitive Line rats (bred for their hyperresponsiveness to cholinergic stimulation, thus representing an animal model of depression) on a forced swim test. Djuric, Dunn, Overstreet, Dragomir, and Steiner (1999) found that, regardless of whether rats were "depressed," those that ingested nicotine for 14 days exhibited far fewer depressive-like behaviors (less immobility on a forced swim test) relative to rats who were not exposed to nicotine or who were exposed to nicotine for shorter periods of time. These findings are therefore consistent with the argument that nicotine may be a more effective antidepressant than an anxiolytic (Balfour, 1991; Balfour & Ridley, 2000).

Anger and Aggression

Several early animal investigations suggest that nicotine specifically suppresses aggressive responding in ants (Kostowski, 1966), cats (Bernston, Beattie, & Walker, 1976), rats (Driscoll & Baettig, 1981; Rodgers, 1979; Waldbillig, 1980), and monkeys (Hutchinson & Emley, 1973). Moreover, it appears that these findings were not due to nonspecific or generalized depressant actions of nicotine. Similar findings have been reported in laboratory studies with humans (e.g., Acri & Grunberg, 1992; Cherek, 1981; Girdler, Jamner, Jarvik, Soles, & Shapiro, 1997; Jamner, Shapiro, & Jarvik, 1999; Schechter & Rand, 1974). Of consequence, two of these studies reported that nicotine reduced anger in both smokers and

nonsmokers (Girdler et al., 1997; Jamner et al., 1999), suggesting that these effects are not due solely to withdrawal alleviation.

Summary

In the maintenance stage, there appears to be a strong between-subjects association between a variety of indices of stress and NA and smoking status. Thus, as was observed with smoking initiates, smokers in the maintenance stage are significantly more likely to experience many forms of stress and NA relative to nonsmokers. Again, however, one cannot infer that stress and NA leads to smoking on the basis of these findings alone. It is also possible that smoking itself, withdrawal from smoking, or a combination of the two creates the heightened levels of stress and NA often reported by smokers. However, within-subject findings of increased smoking following negative life events, as well as in response to laboratory stressors, undermine the smoking-causes-stress argument.

With respect to whether smoking and nicotine genuinely reduce subjective stress and NA, findings from both the animal and human literature are quite variable. Among the various manifestations of NA and stress, depressive symptoms emerge as the strongest between-subjects correlate of smoking behavior. However, it is notable that no human laboratory studies have yet assessed nicotine's effect on feelings of dysphoria and sadness. Mixed findings regarding the effects of smoking on stress and NA may be attributable to methodological variance and/or measurement error. One interpretation of the inconsistent findings, however, is that if cigarette smoking does alleviate stress and NA, it does so indirectly or in interaction with other factors and not through some direct pharmacologic effect (see Steele & Josephs, 1990). An implication of such a hypothesis is that rather than asking whether smoking and nicotine reduces stress and NA, perhaps investigators should be looking for moderators and mediators of these relationships.

Several candidate factors worthy of further consideration include: stressor features, dosing parameters, temporal proximity, route of administration, individual differences, and types of emotional response. Gilbert (1995) proposed that features of the stressor itself govern whether nicotine assuages NA, positing that when consumed in the presence of distal, ambiguous, and anticipatory stressors (e.g., Gilbert et al., 1989), nicotine tends to reduce NA, whereas in the presence of proximal stressors (e.g., Fleming & Lombardo, 1987), it does not. Kassel and colleagues (Kassel & Shiffman, 1997; Kassel & Unrod, 2000) have argued that a contextual variable—the presence or absence of benign distraction—moderates nicotine's effects on anxiety. Dosing parameters also emerge as an important variable that is difficult to control in human smoking. Animal studies reveal marked differences across doses with respect to nicotine's influence on anxiety (e.g., Cheeta, Irvine, Tucci, et al., 2001; Faraday et al., 2001), with some dose-response effects being nonlinear. Given that there is reason to believe that the effects of smoking and nicotine are relatively transient, at least in humans (Perkins, Grobe, Fonte, & Breus, 1992), temporal proximity to dosing becomes critical in determining how, or whether, nicotine affects emotional response; that is, how soon after dosing one assesses emotional response is impor-

tant.⁶ Correspondingly, different routes of nicotine administration (e.g., inhalation, subcutaneous, oral) result in markedly different pharmacokinetic profiles that likely modify nicotine's influence on emotion. At the level of individual differences, a host of candidate variables can be considered, among them neuroticism, trait anxiety, negative affectivity, impulsivity, and gender (see Gilbert, 1995, for a review). Finally, variability across studies in the dependent variable—emotional response—certainly must be considered as potentially contributing to inconsistent findings. Indeed, whether smoking and nicotine differentially influence anxiety, depression, boredom, or anger, for example, has yet to be systematically addressed. Moreover, even when ostensibly assessing the same emotion (e.g., anxiety), different measurement strategies have been used, resulting in different findings (e.g., File, Cheeta, & Kenny, 2000). In the end, it is likely that delineating the complex relationship between smoking and affect demands consideration of these various factors and more.

Smoking Relapse

Relapse: Do Stress and NA Promote Smoking?

Relapse is the modal outcome among those attempting to quit smoking (e.g., Garvey, Bliss, Hitchcock, Heinold, & Rosner, 1992; Shiffman, 1982; see also Brigham, Henningfield, & Stitzer, 1991). The link between stress and NA and relapse has been examined at the between-subjects level of prequit individual differences. Here, we find that the presence of clinically significant levels of NA is often predictive of relapse (Glassman et al., 1990; Hall, Muñoz, Reus, & Sees, 1993). For instance, one study (Anda et al., 1990) reported that the likelihood of quitting smoking was 40% lower among depressed smokers compared with nondepressed smokers. Glassman et al. (1990) reported a quit rate of 14% for study subjects meeting criteria for major depression, whereas 31% of subjects with no psychiatric diagnosis successfully quit. In the absence of current symptomatology, history of depression appears to heighten risk for both relapse (Covey, 1999) and recurrence of depressive symptomatology subsequent to cessation (Covey, Glassman, & Steiner, 1997). These effects may be even more pronounced among women (Borrelli, Bock, King, Pinto, & Marcus, 1996).

Several studies have examined the extent to which smokers who attribute their smoking to NA reduction (via self-report questionnaires) are at heightened risk to relapse. O. Pomerleau, Adkins, and Pertschuk (1978) found that at 1-year follow-up, NA-reduction-motivated smoking was the only variable that predicted smoking status. O'Connell and Shiffman (1988) similarly reported that NA-reduction-motivated smoking was a significant predictor of outcome at 12 months. Moreover, NA-reduction-motivated smokers were more likely to report that their relapse crises were precipitated by NA.⁷ It is important to note that NA smoking scores are positively related to smoking rate (see Shiffman, 1993). By implication, NA smoking scores may serve as an indirect proxy for both nicotine dependence, an established predictor of smoking relapse (e.g., Breslau & Peterson, 1996; Killen et al., 1996), and depressive symptoms. Hence, the construct validity of measures assessing NA smoking has been called into question (Shiffman, 1993).

Stemming from attempts to better understand the factors governing smoking relapse, numerous within-subject studies have

implicated the role played by stress and NA. Thus, based on a variety of retrospective, self-report methodologies, anywhere from 35%–100% of smokers report that they lapsed while experiencing some form of stress or NA (e.g., Borland, 1990; Brandon, Tiffany, Obremski, & Baker, 1990; Cummings, Jaen, & Giovino, 1985; Shiffman, 1982; Swan et al., 1988).

In an attempt to address the methodological limitations inherent in studies using retrospective self-report, Shiffman and colleagues asked smokers who were attempting to quit smoking to use palm-top computers and record, in near real time, the situational and affective antecedents of their smoking lapses. Findings from these within-subject studies indicate that lapses were accompanied by NA more so than were temptations (strong urge, but no lapse) and that temptations were preceded by NA more so than were random nonsmoking situations (Shiffman, Paty, Gnys, Kassel, & Hickox, 1996). Moreover, those whose lapses were triggered by stress (but not by "bad mood") progressed more quickly to another lapse (Shiffman, Hickox, et al., 1996).

In summary, the within-subject association between stress and NA and smoking lapses appears fairly robust. A convergence of findings strongly points to an association between various manifestations of NA and smoking relapse. Moreover, from a between-subjects perspective, a variety of prequit individual differences related to NA, particularly depression, have demonstrated predictive validity.

Relapse: Does Smoking Reduce Stress and NA?

Although there have been few direct assessments of the effects of smoking and nicotine among those in the midst of relapse, some interesting data do bear on this issue. Brandon et al. (1990) asked smokers who smoked subsequent to participating in a cessation program to describe their affective reactions to their initial lapse. Whereas almost 50% described feeling depressed or hopeless, 16% described feeling anxious or tense, and 10% described feeling angry or irritated, only 8% reported feeling relaxed and 6% felt happy, celebratory, or confident. A limitation of these data is that they are retrospective accounts of what were likely fleeting experiences. Using palm-top computers to assess real-time affective antecedents and consequences of smoking lapses, Shiffman et al. (1997) reported that whereas lapses resulted in increases in NA, temptation episodes did not. Correspondingly, relative to temptations, lapses almost inevitably resulted in significant drops in self-efficacy and increases in feelings of guilt and discouragement.

Consistent with the argument that context and other nonpharmacological factors may influence smoking's effects on emotional

⁶ Methods best suited to capturing the brief life span of smoking's effects on mood include controlled laboratory investigations and controlled field studies using real-time self-monitoring techniques (see Methodological Considerations section).

⁷ Several studies have reported that differences in physiological reactivity to stress and smoking-related cues are associated with subsequent smoking relapse. Swan, Ward, Jack, and Javitz (1993) found that higher levels of systolic blood pressure reactivity to a prequit cognitive challenge was associated with a shorter time to relapse. Two other studies using a smoking-related cue-exposure paradigm found that prospective quitters had significantly less heart rate reactivity in response to the cues (Abrams, Monti, Carey, Pinto, & Jacobus, 1988) and that relapsers exhibited a sharp heart rate deceleration (Niaura, Abrams, Demuth, Pinto, & Monti, 1989).

response, the findings that smoking lapses appear to exacerbate NA likely reflect, at least in part, an *abstinence violation effect*. The abstinence violation effect refers to a frequently observed constellation of negative emotions and disparaging self-evaluation that follows a transgression of one's commitment to abstinence (see Marlatt & Gordon, 1985).

Another interesting perspective on whether smoking reduces stress and NA comes from studies examining the time course of stress and NA among those who successfully quit smoking. Almost all of these studies report that, although there is usually an initial increase in stress and NA subsequent to cessation, these symptoms diminish over time to levels lower than observed prior to quitting (Carey, Kalra, Carey, Halperin, & Richards, 1993; Cohen & Lichtenstein, 1990; Hughes, 1992; R. West & Hajek, 1997; though see Gilbert et al., 2002). Moreover, smokers who are unable to maintain abstinence generally continue to manifest high levels of stress and NA over time (Carey et al., 1993; Cohen & Lichtenstein, 1990). By implication, it has been suggested that whereas smoking engenders stress and NA (Parrott, 1999), quitting results in lower stress and NA over time.

Summary

Table 2 is a presentation of the findings reviewed in the previous sections. From a between-subjects level of analysis, smokers have been consistently shown to experience heightened levels of stress and NA relative to nonsmokers. Across both animal and human studies, and across the initiation and maintenance stages of smoking, evidence suggests that self-reported stress (as assessed in a number of ways) and NA (also assessed by various methods) are linked to smoking status and propensity to self-administer nicotine. Although these observed between-subjects correlations invite warranted speculation as to underlying causal mechanisms, such inferences must be tempered both by the observation that reverse causality (e.g., smoking predisposes to depression) likely accounts for some of the variance in the relationship and by the findings from longitudinal studies suggesting that shared etiologies may predispose to both NA and smoking.

An even more inconsistent picture emerges when addressing the within-subject questions posed at the outset of this article. First, whereas the extent to which stress and NA genuinely cue smoking remains virtually unknown among smoking initiates, some studies suggest that affective distress does cue smoking among regular smokers, and stress and NA appear to often precede lapses among those trying to quit. At the same time, when cueing of smoking is considered within the context of a longer time frame, some (but not all) studies indicate that NA does predispose one to begin smoking (the initiation phase). Finally, the other within-subject question asked whether smoking actually reduces stress and NA. The effects of smoking and nicotine on the emotional response of those in the initiation stage remain virtually unexplored. Findings from studies assessing the effects of smoking and nicotine on regular and dependent smokers in the maintenance stage yield very mixed results. Smoking and nicotine appear capable of reducing various forms of NA and stress (independently of withdrawal relief), but they do so quite inconsistently. Finally, although the effects of smoking among those in relapse has not received much empirical attention, extant data suggest that smoking lapses lead to worsened

emotional states and that successful quitters actually experience less stress and NA subsequent to quitting.

Perhaps the most striking aspect of these findings is the dearth of information regarding the smoking initiation phase. Other than an observed association of depression and externalizing disorders with smoking initiation, virtually nothing is known about the causes and effects of smoking among initiates (most often, adolescents). Given the profound health implications of adolescent smoking (e.g., Lam, Chung, Beison, Wong, & Hedley, 1998), delineation of the reinforcing mechanisms underlying adolescent smoking should be of paramount importance to future research endeavors.

Finally, the inconsistent findings with respect to the effects of smoking on stress and NA suggest that more emphasis should be placed on the identification of potential moderators and mediators of smoking–stress–affect relationships. In the sections that follow, we review a number of models purporting to explain some of the processes governing the effects of smoking on stress and NA, as well as those governing the effects of stress and NA on smoking.

MECHANISMS

Numerous hypothesized mechanisms underlying the links between stress and NA and smoking have been described previously (e.g., Brandon, 1994; Gilbert, 1979, 1995; Gilbert & Welser, 1989; Hall et al., 1993; Kalman, 2002; Parrot, 1994; Piasecki & Baker, 2000; O. F. Pomerleau & Pomerleau, 1991; USDHHS, 1988). Although a comprehensive examination of all proposed mechanisms is beyond the scope of this review, we focus briefly on the following aspects of the association between smoking and affective distress. The first aspect we review is based on the classic explanation—that people smoke when stressed because smoking does relieve stress and NA. We review several different models attempting to explain how nicotine administration and smoking might lead to reductions in stress and NA. These approaches include direct-effect, moderator, and mediator models. As shown in Table 3, direct-effect mechanisms, in theory, apply to all stages of smoking because stress alleviation is one motive that can conceivably explain smoking initiation, maintenance, and relapse. Similarly, except as where noted otherwise, the moderator and mediator models also apply to all stages of smoking.

We then examine several models that may help explain why stress and NA may promote (i.e., cue) nicotine use even in the absence of true emotion-modulating effects. The applicability of these models to the stages of smoking are discussed below.

Direct-Effect Models of Smoking's Effects on Stress and NA

Endogenous Opioids

Given opioids' known euphoric, analgesic, and potentially anxiolytic properties, it has been proposed that nicotine may alleviate the aversive effects of stress and NA through an opioid mechanism (Balfour, 1991; O. F. Pomerleau, 1998; O. F. Pomerleau & Pomerleau, 1984). In a test of this hypothesis, Gilbert, Meliska, and Plath (1997) investigated the effects of noise stress and smoking on peripheral beta endorphins in habitual smokers. Although noise

Table 3
Summary of Models of Potential Mechanisms Governing Nicotine–Affect Associations and Their Potential Applicability Across Smoking Stages

Model	Comments	Applicability across smoking stages		
		Initiation	Maintenance	Relapse
Direct-effect models proposing smoking alleviates stress & NA				
Endogenous opioids	Few supportive data	Yes	Yes	Yes
Restoration of homeostasis (corticosteroids)	Few supportive data	Yes	Yes	Yes
Reward pathways (dopamine)	Few supportive data	Yes	Yes	Yes
Mediator and moderator models of smoking's influence on stress & NA				
STAR	Promising initial findings; needs more empirical confirmation	Yes	Yes	Yes
Other individual differences	Inconsistent findings; warrants more study	Yes	Yes	Yes
Attentional mediational	Promising initial findings	Yes	Yes	Yes
Enhanced cognitive performance	Few supportive data	Yes	Yes	Yes
Social facilitation	Few supportive data	Yes	Yes	Less likely
Models explaining effects of stress & NA on smoking				
Nicotine withdrawal escape	Strong evidence, but clearly can't explain smoking initiation	No	Yes	Can better explain early (vs. late) relapses
Expectancy effects	Promising initial findings	Yes	Yes	Yes
Changes in nicotine sensitivity and availability	Few supportive data	Unlikely	Yes	Unlikely
Cross-sensitization of dopamine pathways by stress & nicotine	Promising initial findings	Yes	Yes	Perhaps
Allostasis of reward and stress systems	In need of more empirical substantiation	Yes	Yes	Yes

Note. NA = negative affect; STAR = Situation × Trait Adaptive Response.

was associated with modest increases in beta endorphins, nicotine did not change plasma beta endorphin levels beyond those induced by the noise stressor, as would be expected if nicotine alleviated the aversive effects of stress through an opioid mechanism. Moreover, and inconsistent with previous studies, nicotine alone did not increase peripheral beta endorphins. Thus, the available evidence (this single study) does not show a potentiating effect of nicotine on stress-induced peripheral beta endorphin release. However, as this study focused on peripheral opioids, its relevance to central opioid mechanisms is not clear. Direct effects of nicotine on central stress-induced opioids, then, remain to be tested. It is interesting to note, however, that although opioids may not directly alleviate the aversive effects of stress, there is evidence that they may prime the dopaminergic system, which, in turn, may render nicotine more reinforcing (George, Verrico, Xu, & Roth, 2000; Hutchison, Collins, Tassej, & Rosenberg, 1996). Finally, future investigations should consider a wider range of endogenous opioid types (e.g., dynorphins, enkaphalins) as potential mediators of smoking–stress–NA relationships. In sum, although the role of nicotine-induced increases in opioids in directly alleviating the aversive effects of stress appears equivocal, there is some evidence that opioids may prime the dopaminergic system, rendering nicotine more reinforcing.

Reward Pathways

Recent evidence implicates the mesolimbic DA system in reinforcement from nicotine via nicotinic acetylcholine receptor pathways (Dani & Heinemann, 1996; Epping-Jordan, Watkins, Koob, & Markou, 1998; Picciotto et al., 1998). Given the involvement of mesolimbic dopaminergic pathways in drug reinforcement and incentive salience (Berridge & Robinson, 1998; Koob & Le Moal, 1997; Wise, 1998), another potential direct-effect mechanism involves nicotine's effect on these pathways (Balfour, 1991; O. F. Pomerleau & Pomerleau, 1984).

We know of only a handful of studies examining the effects of stress and nicotine on DA release (George et al., 1998, 2000; Pawlak et al., 2000; Serova, Danailov, Chamas, & Sabban, 2000; Takahashi, Nagai, Tetsumei, & Takada, 1998). Effects were variable, ranging from nicotine attenuation of stress-induced gene expression of DA precursors in the ventral tegmental area of the mesolimbic DA pathway with large doses of nicotine (Serova et al., 2000) to nicotine augmentation of nucleus accumbens DA utilization following pretreatment with smaller nicotine doses (George et al., 2000). Other studies have demonstrated effects of nicotine on DA levels and their utilization in the mesoprefrontal cortex (George et al., 1998, 2000), the striatum (Pawlak et al.,

2000; Takahashi et al., 1998), and the locus coeruleus (Serova et al., 2000). Similar to effects of nicotine and smoking on stress, differences are likely due to mode and dosing of nicotine administration, rat strain, and type and duration of stress across studies. Thus, the available evidence is equivocal regarding mesolimbic DA as a direct-effect mechanism underlying the impact of smoking and nicotine on stress and NA. Further research examining the influence of nicotine on DA responses to stressors varying in type and duration, on DA release versus metabolism, and on patterns of changes in DA release across different pathways (e.g., mesoprefrontal, nigrostriatal) is warranted. In addition, the effects of DA changes following nicotine administration on behavioral and affective responses to stress will be critical in determining consequences of nicotine and stress-induced DA variations.

Restoration of Homeostasis (Corticosteroids)

Munck, Guyre, and Holbrook (1984) have proposed that one function of corticosteroids is to dampen the sympathetic component of the stress response, thus returning the stress system to homeostasis. Given that nicotine and smoking increase corticosteroid levels (Benwell & Balfour, 1979; Gilbert et al., 1992; Kirschbaum et al., 1992; Seyler, Fertig, Pomerleau, Hunt, & Parker, 1984), O. F. Pomerleau and Pomerleau (1991) hypothesized that increases in corticosteroid levels from nicotine might dampen sympathetic responses, thus reducing a potentially aversive component of the stress response. Little empirical evidence supports this hypothesis. In fact, the handful of studies that have allowed for a test of this hypothesis suggests that nicotine appears to potentiate both the corticosteroid and sympathetic components of the stress response. Morse (1989) found in a study of rabbits that, although nicotine potentiated the HPA response to stress, it also potentiated the catecholamine response to stress. Similarly, in humans, nicotine has been found to additively increase both cortisol and sympathetic responses to psychological stress (Dembroski, MacDougall, Cardozo, Ireland, & Krug-Fite, 1985; Perkins, Epstein, Jennings, & Stiller, 1986; C. S. Pomerleau & Pomerleau, 1987; O. F. Pomerleau & Pomerleau, 1990). Another possibility is that chronic smoking, rather than an acute nicotine burst, might dampen sympathetic responses to stress through increases in corticosteroids. However, in most studies, smokers appear to show attenuated cortisol responses compared with nonsmokers (Kirschbaum et al., 1993, 1994; Tsuda, Steptoe, West, Fieldman, & Kirschbaum, 1996), as well as heightened or similar sympathetic output (Davis & Matthews, 1990; Perkins, Grobe, Fonte, & Breus, 1992; Roy et al., 1994; Tsuda et al., 1996). Thus, there is little support for the notion that acute or chronic nicotine- or smoking-induced increases in corticosteroids reduce the sympathetic component of the stress response. Indeed, recent research suggests that corticosteroids may permit or enhance, as well as dampen, sympathetic responses to stress (Koob & Le Moal, 2001; Sapolsky et al., 2000).

Summary

None of the direct-effect models reviewed (endogenous opioids, corticosteroid, and reward pathways) offers a definitive answer to the question of smoking's influence on affective distress. It may be that other factors (e.g., environmental setting, cultural influences,

specificity of the emotional state) must be considered in order to fully understand these relationships. Indeed, this review of the literature reveals that, with some notable exceptions (e.g., Gilbert & Gilbert, 1998; Kassel & Shiffman, 1997), very few mediator and moderator models of smoking's effects on emotional response have been put forth. This is likely due to the enduring search for direct-effect explanations for nicotine-affect interactions. Acknowledging the paucity of studies in this area, we now review several moderator and mediator approaches to the smoking-affect problem.

Mediator and Moderator Models of Smoking's Effects on Stress and NA

Situation × Trait Adaptive Response (STAR) Model

Probably the most ambitious attempt to explain smoking behavior and its impact on affective processing has been offered by Gilbert (1995; Gilbert & Gilbert, 1998). Working from the premise that most of the affect-modulating and reinforcing effects of nicotine are indirect, he proposed a model (Gilbert & Gilbert, 1998) that includes multiple potential mediators and moderators of the nicotine-NA relationship. In the model, it is asserted that variability in response to nicotine can be attributed, in part, to both situational determinants (e.g., nature of the stressor) and individual differences in trait adaptive responses. In Gilbert's (1995) view, trait adaptive responses include personality traits, coping styles, and psychopathology. Examples of personality traits believed to moderate the effects of nicotine on emotional response include neuroticism, depression, extraversion, psychoticism, impulsivity, unconventionality, and antisocial behavior. Thus, it is believed that nicotine reverses or ameliorates the affective states associated with each of these domains.

The STAR model also postulates that nicotine influences internally driven—for example, memory-, associative-, and attention-based—processes more so than externally driven processes (e.g., exposure to stimuli associated with rigid stimulus-response associations), such that

in situations characterized by cues suggestive of future threat and those utilizing ambiguous cues requiring substantial associative elaboration to generate threat, nicotine attenuates negative affect by altering internally driven associative processes, while in others it promotes goal achievement by its attentional and performance-enhancing effects and thereby indirectly modulates mood states. (Gilbert & Gilbert, 1998, p. 141)

In support of these assertions, the literature reveals that (a) nicotine can enhance performance and goal attainment independently of withdrawal relief (Kassel, 1997; Wesnes & Parrott, 1992); (b) nicotine's tranquilizing effects occur primarily when stressors are distal and anticipatory (this is based, in part, on the assumption that the smoking situation itself provides distraction from anxiety provoking cues; see also Kassel, 1997; Kassel & Shiffman, 1997); (c) nicotine can reduce approach-avoidance conflict-generated affective distress by raising the approach gradient as well as by reducing the avoidance gradient; and (d) nicotine increases left-frontal (cholinergic and dopaminergic) cortical activation, thereby enhancing controlled processing, approach mechanisms, and left-hemisphere-dominant positive affect associative networks.

In sum, the STAR model is ambitious in its attempt to explain smoking's influence not only on emotional response but also on other nicotine-related reinforcement processes as well. It is important because it attempts to answer both between- and within-subjects issues regarding smoking-affect relationships. Although its many propositions and corollaries (too numerous to capture in this article) are compelling, they are in need of further empirical substantiation.

Other Individual Differences

There are numerous potential individual difference variables, some of which have already been touched on in this review, that might moderate smoking's effects on emotional response. Until these between-subjects factors are more clearly articulated, one must assume that they are equally applicable across the initiation, maintenance, and relapse stages. One of the more influential moderator models was put forth by Eysenck (1973), who claimed that people smoke, in part, as a way of modulating arousal level. The basic premise rests on the belief that smoking exerts arousing effects when the smoker is emotionally or mentally understimulated and exerts dearousing, or calming effects, when cortical arousal is high, such as during states of emotional excitation. Thus, extraverts, who are characterized by chronic underarousal, are thought to smoke more often to achieve pleasurable stimulation of the primary reward centers, whereas introverts and neurotic individuals, who are predisposed to high arousal levels, are believed to smoke more often in order to achieve lower central nervous system arousal via negative reinforcement systems. A related hypothesis, that small doses of nicotine increase cortical and subjective arousal whereas larger doses result in suppression of arousal, has received some support from animal studies (e.g., Armitage, Hall, & Morrison, 1968) but relatively little substantiation from human studies (see Church, 1989; R. J. West, 1990). In sum, the notion that nicotine influences emotional response by means of its effects on arousal modulation is still an important one warranting further investigation, particularly within a framework of emotion that draws on both affective valence and arousal components as contributing to emotional response.

Based, in part, on the findings that women often attribute their smoking to affect-regulation motives more so than men (e.g., Ikard et al., 1969; Spielberger, 1986) and that women find quitting more difficult than men (Wetter et al., 1999) is the emergence of sex as a potential moderator of nicotine's effects on emotional response. Moreover, Wetter et al. (1999) found that stress was more strongly (negatively) associated with cessation among men than women. In the end, however, there is little evidence to support the notion that smoking and/or nicotine differentially affect emotional response in men and women. Although Perkins, Grobe, Fonte, and Breus (1992) found that observed anxiolytic effects of nicotine were more transient for men than for women, other studies detected no sex differences in the effects of smoking on anxiety responses to stressful movies (Gilbert & Hagen, 1985; Gilbert et al., 1989). More recently, Eissenberg, Adams, Riggins, and Likness (1999) assessed sex differences in several physiological and subjective effects of smoking, finding only that the reduction in craving produced by smoking was greater in women than in men and that women take smaller and shorter puffs than men. In their review of the sex differences literature, Perkins, Donny, and Caggiola (1999)

concluded that women's smoking may be influenced more by non-nicotine stimuli associated with smoking, perhaps indicative of heightened conditioned reinforcement of smoking in women. Moreover, there is reason to believe that women may be less sensitive to some effects of nicotine that may be reinforcing. More research is clearly needed to assess the consistency of these findings across human and animal subjects, as well as to determine the specific aspects of reinforcement that may differ between men and women.

Attentional Mediation Model

On the basis of the belief that nicotine has no direct effect on NA, Kassel (1997; Kassel & Shiffman, 1997) proposed that smoking affects anxiety and other emotional states indirectly through its reliable effects on attentional narrowing (a notion that, although it differs slightly in its proposed mechanisms, is consistent with Gilbert's [1995] STAR model). Drawing from Steele and Joseph's (1988) model of alcohol's effects on emotional response, Kassel (1997) noted that smoking similarly narrows the focus of attention and therefore may reduce anxiety by facilitating distraction from an impending threat. In the first test of this model, Kassel and Shiffman (1997) demonstrated that, as predicted, smoking reduced subjects' anxiety only when paired with a distractor (viewing and rating art slides). In the absence of benign distraction, smoking exerted no effect on anxiety. Among those subjects who were not exposed to the distractor, anxiety remained unchanged regardless of whether they smoked. Thus, the findings could not be explained by direct nicotine effects or nicotine withdrawal (because all smokers were minimally deprived and a nonsmoker control group was also used).

In a follow-up study (Kassel & Unrod, 2000), smokers smoked either a high- or ultralow-nicotine-yield cigarette with or without the presence of benign distraction. A similar pattern of findings emerged such that smokers who smoked the high-nicotine-yield cigarette paired with art slides experienced a large reduction in subjective anxiety, whereas those who smoked the high-yield cigarette in the absence of distraction actually experienced a slight exacerbation of their anxiety (see Figure 1). These findings, therefore, implicate nicotine as the agent in cigarette smoke responsible for attentionally mediated anxiety reduction. Moreover, the results from these studies point to the importance of considering context—in this case, benign distraction—when examining smoking's effects on emotional response. Findings from a series of rat studies (Acri, 1994) similarly suggest that nicotine may dampen the stress response by attenuating the deleterious attentional effects of stress.

Although the attentional mediation model offers some promising initial findings, the extent to which the proposed mechanism is applicable to other negative affective states has yet to be determined. Nor is it clear whether the proposed mechanism is a volitional one, over which the smoker exerts conscious control, or an automatic process of attentional capture. Finally, given that the model identifies situations under which nicotine may diminish NA, it seems equally applicable to the initiation, maintenance, and relapse stages of smoking. Future research based on this kind of a contextual approach to the study of nicotine-NA interactions is clearly warranted.

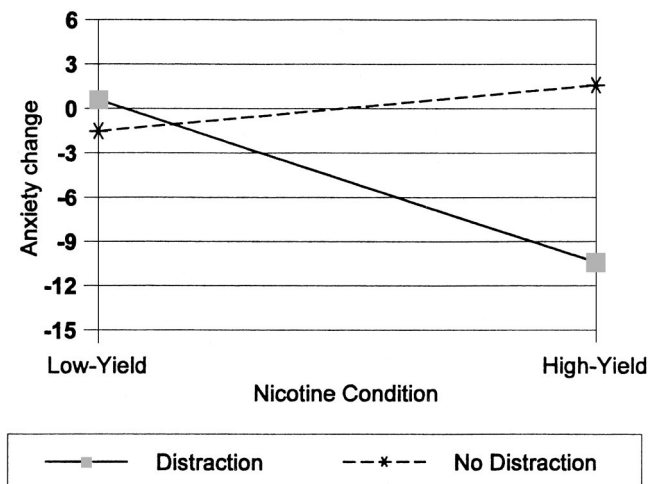


Figure 1. Demonstration that smoking's effects on anxiety change are dependent on both nicotine yield and the presence of benign distraction. Adapted from Figure 1 of "Smoking, Anxiety, and Attention: Support for the Role of Nicotine in Attentionally Mediated Anxiolysis," by J. D. Kassel and M. Unrod, 2000, *Journal of Abnormal Psychology*, 109, p. 164. Copyright 2000 by the American Psychological Association. Those who smoked a high-nicotine-yield cigarette in the presence of benign distraction derived the greatest reduction in anxiety. The portrayed interaction effect was significant ($p = .001$).

Smoking's Effects on Cognitive Performance

Just as the literature on nicotine's effect on affect has produced mixed findings, so too have attempts to characterize nicotine's impact on cognitive processing. Nonetheless, one possible mechanism through which smoking might indirectly assert its effects on NA reduction is through its ability to enhance cognitive performance. Simply stated, as smoking and nicotine enhance cognitive functioning, so too may they alleviate NA attributable to the cognitive challenge. The ultimate problem with this hypothesis is that the field has yet to precisely characterize the nature of nicotine's effects on cognitive processing. Although some evidence suggests that nicotine can be reinforcing through its ability to improve performance on sustained and selective attention tasks (see Kassel, 1997; Koelega, 1993; Wesnes & Parrott, 1992), a host of other data suggest that these effects are elusive (Heishman, Taylor, & Henningfield, 1994), or, in some instances, that nicotine actually leads to detriments in cognitive performance (Spilich, June, & Renner, 1992). Indeed, analogous to nicotine's effects on NA, there is reason to believe that other factors, including differences in dosing and the cognitive demands of the task, likely influence the extent to which nicotine influences attentional processing (see Heishman et al., 1994; Kassel, 1997).

It is important to point out, however, that just as nicotine's effects on emotional response may be indirect, so might its effects on cognition. Waters and Sutton (2000) noted that the associations among affect, cognition, and arousal are, to a great degree, reciprocal, such that each system exerts influence on the others. Although the precise nature of its effects on these systems is still unclear, there is strong reason to believe that nicotine—directly or

indirectly—influences all three. Thus, as smoking may influence emotion through its impact on cognition (Kassel & Shiffman, 1997), it may also exert its effects on affective response through arousal modulation. Conversely, smoking's effects on emotion or arousal could similarly affect its impact on cognition. As such, future research should attempt to model mediational mechanisms of these types far more than has been done to date. This cognitive–mediational approach holds the potential to explain smoking onset, maintenance, and relapse.

Smoking's Effects on Interpersonal Functioning

Numerous findings from studies that use smoking motives questionnaires suggest that smoking as a social tool is a frequently cited reason to smoke (e.g., Ikard et al., 1969; M. A. H. Russell et al., 1974). Although bereft of any empirical validation, the notion that smoking may reduce NA through its potential ability to facilitate social interactions is compelling, especially in the context of smoking initiation among adolescents. Indeed, a wealth of data points to reliably strong associations between peer smoking behavior and smoking initiation (e.g., Krosnick & Judd, 1982; Stanton & Silva, 1992; see also P. West & Michell, 1999). The extent to which this association is reciprocal (peer influence vs. peer selection) has been examined, with results strongly suggesting that peer influence is the more potent of the two mechanisms (e.g., Wills & Cleary, 1999). Nonetheless, very little is known about the mechanisms that underlie the reliable link between peer influence and smoking status. Some theoretical frameworks have suggested that drug use (including cigarette smoking) can serve to reduce feelings of self-derogation (Kaplan, 1978) or to enhance an adolescent's sense of self within particular social contexts (Steffenhagen, 1989). Thus, according to these perspectives, there is reason to believe that smoking might facilitate feelings of self-enhancement in the adolescent smoker. Such a context-driven perspective is useful and should be used to guide future research on the effects of smoking within social situations, particularly among adolescents. Although this model holds the most appeal in explaining smoking initiation and maintenance, it is conceivable that social facilitation motives could also play a role in smoking relapse.

Summary

Working from the premise that smoking's effects on stress and NA may be dependent, at least in part, on other factors, the mediator and moderator approaches reviewed appear to hold promise with respect to better understanding the processes governing smoking–affect relationships. Thus, contextual influences (e.g., social interactions, cognitive challenge, benign distraction) and individual differences (e.g., gender, ethnicity, negative affectivity) warrant further study regarding their role in modifying nicotine's influence on stress and NA. In the following section, we review several models attempting to explain the observed link between smoking and affective distress from perspectives steeped in the belief that smoking may not possess genuine mood modulating effects.

The Effects of Stress and NA on Nicotine Consumption

Nicotine Withdrawal Escape

In some respects, the simplest and most straightforward account of why stress and NA appear to promote smoking is offered by the nicotine withdrawal escape (deprivation reversal) model (Parrott, 1999). Many studies have demonstrated that when a nicotine-dependent smoker abstains from nicotine, a fairly predictable and reliable withdrawal syndrome ensues (see Hughes et al., 1990; Shiffman, 1979). Moreover, the withdrawal comprises various manifestations of NA. Thus, increases in anger and irritability (Hatsukami, Dahlgren, Zimmerman, & Hughes, 1988; Hughes & Hatsukami, 1986), anxiety and tension (Hatsukami, Hughes, & Pickens, 1984; Hughes & Hatsukami, 1986), and dysphoria and depression (Hatsukami et al., 1984; R. J. West, Russell, Jarvis, & Feyerabend, 1984) are frequently experienced by abstinent smokers. Given that administration of nicotine (via cigarette smoke or other forms) appears to reverse these adverse effects (Hughes et al., 1984), the withdrawal escape model posits that smokers derive a reduction in NA only through nicotine's ability to relieve (or stave off) withdrawal symptomatology, not through some inherent ability to transform affective states (Parrott, 1999).

A variant of this proposition suggests that smokers, through repeated pairing of withdrawal-induced affective distress and smoking-induced alleviation of distress, come to view various affective states such as anxiety and dysphoria as discriminative stimuli signaling that smoking will be reinforcing (O. F. Pomerleau & Pomerleau, 1984). Put simply, NA may become a cue for smoking even when it occurs independently of nicotine withdrawal. Whereas the nicotine withdrawal escape model cannot explain smoking initiation (as the emergence of a withdrawal syndrome takes time), it is the most widely held model with respect to explaining smoking maintenance. Its applicability to understanding relapse is primarily limited to early lapses, although if one invokes conditioning processes, then withdrawal-conditioned cues could lead to relapse long after the smoker has quit.

Expectancy Effects

A large literature, particularly within the area of alcohol consumption, has shown that individuals' expectations of drug effects can have profound effects on motivational and drug-seeking processes (e.g., Cox & Klinger, 1988; Goldman, Del Boca, & Darkes, 1999). According to this perspective, it is conceivable that the association between smoking and stress and NA is epiphenomenal, steeped in the belief, but not necessarily the reality, that smoking assuages negative mood. Although there has been little research on expectancy effects and smoking, there are some informative findings (see Brandon, Juliano, & Copeland, 1999, for a review).

Bauman and Chenoweth (1984) assessed the expected consequences from smoking cigarettes among 1,400 adolescents, only a small proportion of whom had ever smoked. Analyses revealed that the negative physical and social consequences factor predicted smoking initiation, whereas the pleasure factor (e.g., "Smoking will make me feel more relaxed") predicted both initiation and increased smoking among those who were smokers at the study's onset. Chassin, Presson, Sherman, and Edwards (1991) found that

strong positive beliefs about the psychological consequences of smoking predicted smoking onset during both adolescence and adulthood. Moreover, expectation of NA reduction, as assessed by the Smoking Consequences Questionnaire (Brandon & Baker, 1991; Copeland et al., 1995), was found to be a potent predictor of end-of-treatment outcome (Wetter et al., 1994).

A different, yet conceptually related, literature on smoking motives has also reliably revealed the presence of a NA motive for smoking, consistent with the observations that almost all adult smokers attribute their smoking, at least in part, to its reputed calming and anxiolytic effects (Frith, 1971; Spielberger, 1986). Numerous studies using factor analysis have pointed to NA reduction as a common motive for smoking, particularly among adult smokers (e.g., Best & Hakstian, 1978; Ikard et al., 1969; McKenell & Thomas, 1967; M. A. H. Russell et al., 1974; Spielberger, 1986).⁸

In sum, a wealth of anecdotal data coupled with self-report questionnaire data suggest that most smokers believe smoking helps to reduce NA. Hence, even in the absence of genuine stress-reducing properties, this expectancy is one possible mechanism through which the link between smoking and NA can be understood. Expectations of NA reduction could potentially explain smoking in the initiation, maintenance, and relapse stages.

Changes in Nicotine Sensitivity and Availability

Stress and NA may reduce sensitivity to and/or the bioavailability of nicotine, resulting in a compensatory increase in nicotine consumption. It is important to note that these mechanisms likely apply only to the maintenance stage of smoking, as individuals must smoke with regularity to experience decreases in bioavailability or sensitivity to nicotine sufficient to actually increase smoking behavior.

Regarding changes in sensitivity, two studies have shown a stress-induced subsensitivity to nicotine, as measured by a reduction in typical behavioral responses in rats. In one, rats showed decreased hypothermic responses to nicotine following forced swimming stress relative to baseline (Peck, Dilsaver, & McGee, 1991), whereas the other study found that rats manifested decreased hypothermic responses following chronic injection stress (Flemmer & Dilsaver, 1989).

With respect to nicotine availability during stress and NA, two primary mechanisms have received attention: Increases in hepatic metabolism and increases in renal clearance. Only one study examined the effects of stress on hepatic metabolism of nicotine (Winders, Grunberg, Benowitz, & Alvares, 1998); the authors found that in laboratory rats, although stress lowered plasma nicotine levels, it did not change conversion of nicotine to cotinine, a measure of hepatic clearance. Thus, although nicotine levels changed during stress, hepatic clearance does not appear to be a viable mechanism underlying these changes. Several studies have shown an increase in urine acidity during stress (e.g., Sandin &

⁸ It is important to note that the scores comprised by the Negative Affect factor in such analyses can often come from questionnaire items that ask about affective antecedents of smoking (e.g., Do you smoke when feeling anxious?) rather than consequences (see Shiffman, 1993). Thus, the extent to which one can infer functional significance from the association between NA and smoking is quite limited.

Chorot, 1985). Others have demonstrated a relationship between increased urine acidity and (a) increased nicotine clearance (Benowitz & Jacob, 1985), (b) increased nicotine consumption (Benowitz & Jacob, 1985; Latiff, Smith, & Lang, 1980), and (c) reduction in the behavioral effects of nicotine (Grunberg, Morse, & Barrett, 1983). Thus, it is conceivable that a stress-induced increase in renal clearance (via increased urine acidity) may reduce availability of nicotine, resulting in increased nicotine consumption. In support of this notion, Schachter, Kozlowski, and Silverstein (1977) found that both urine acidification and smoking increased under stress. In a second, more definitive study, Schachter, Silverstein, Kozlowski, Herman, and Liebling (1977) found that when urinary acidification under stress was eliminated (by maintaining urinary pH at alkaline levels), stress did not result in increased smoking. Although these findings are suggestive, it is unlikely that the modest changes in pH resulting from stress are enough to fully explain changes in smoking behavior under stress. In sum, although more research is needed to determine the implications of these findings, some evidence does suggest that stress results in changes in both nicotine sensitivity and renal nicotine clearance.

Cross-Sensitization of Dopaminergic Pathways by Stress and Nicotine

Similarities in physiological and neural responses to both stress and drugs of abuse (e.g., increases in sympathetic and HPA responses and, particularly, increases in mesolimbic DA release) have led to the hypothesis that stress may sensitize, or prime, pathways to make drugs more reinforcing. Sensitization is a process by which progressively greater neuronal or behavioral responses can be induced by repeated, intermittent administration of a stimulus (e.g., Kalivas & Stewart, 1991). If stress and nicotine target similar neural pathways, it is possible that prior exposure to stress may cross-sensitize pathways underlying reinforcement from nicotine (Piazza, Deminiere, Le Moal, & Simon, 1990; Sorg & Kalivas, 1991). This mechanism might explain the role of stress in initiation (early stress would prime pathways to make nicotine more reinforcing to initiate), maintenance (under stress, smokers would find nicotine more reinforcing), and possibly relapse (ex-smokers would be more vulnerable to relapse during stress because nicotine is more reinforcing during these times) stages of smoking.

Converging evidence suggests that this may be a viable mechanism. There is reason to believe that stress and nicotine independently activate similar DA pathways and that nicotine's effects on both locomotor activation and DA release can be sensitized (Clarke & Kumar, 1983; Olausson, Engel, & Soderpalm, 1999; Panagis, Nisell, Nomikos, Chergui, & Svensson, 1996; but see Bozarth, Pudiak, & KuoLee, 1998). In addition, several studies have demonstrated cross-sensitization (e.g., reinforcement, behavioral responses) between nicotine and other drugs of abuse that themselves have been shown to cross-sensitize stress pathways (Horger, Giles, & Schenk, 1992; Kuribara, 1999; Shippenberg, Heidbreder, & Lefevour, 1996; but see Schenk, Snow, & Horger, 1991). However, as we know of no studies examining cross-sensitization between nicotine and stress directly, this mechanism remains speculative. Future research might examine the effects of prior stress on DA and behavioral responses to nicotine or on the speed in which animals learn to self-administer nicotine. Human

studies examining the effects of prior stress on behavioral and physiological responses to nicotine as well as on progression to nicotine dependence are also warranted. Finally, given the body of research suggesting that stress-induced corticosterone release may underlie cross-sensitization between stress and psychostimulants (Deroche et al., 1995; Piazza et al., 1991; Rouge-Pont, Marinelli, Le Moal, Simon, & Piazza, 1995; but see Prasad, Ulibarri, Kalivas, & Sorg, 1996), further animal and human research examining the role of glucocorticoids in cross-sensitization between stress and nicotine could prove instructive. However, an important caveat of this model is that these mechanisms may not be specific to nicotine and smoking; cross-sensitization may prime pathways underlying reinforcement from numerous drugs of abuse.

Allostasis of Reward and Stress Systems

Koob and Le Moal (2001) have proposed that transitions from drug use to dependence involve changes in hedonic set point involving both reward and stress systems. Allostasis describes a process of maintaining stability outside of the normal homeostatic range, in which all systems arrive at a new set point to cope with chronic stress (Sterling & Eyer, 1988). Koob and Le Moal (2001) hypothesized that addiction involves a change in drug reward set point that reflects an allostatic rather than a homeostatic adaptation (i.e., outside the normal set point). Thus, the initial hedonic effects of the drug are opposed by ever-growing counteradaptive mechanisms (including recruitment of brain and peripheral stress systems; Koob & Le Moal, 1997; Solomon & Corbit, 1974). We believe allostatic mechanisms may play a role across all stages of addiction. Drug initiation may be influenced by the extent to which individuals possess, through genetic or environmental influences, biological vulnerability in the stress and/or reward systems involved in the allostatic state of addiction. In the maintenance phase, dependence itself shifts the stress and reward systems into an allostatic state. Following cessation, the allostatic state likely endures long after acute withdrawal has ended, thus rendering the individual more vulnerable to relapse. Koob and Le Moal (2001) suggested that the neural substrates of allostasis include CRF, DA, and glucocorticoids as well as opioids and serotonin.

Although little research has directly examined allostasis as a mechanism underlying the relationship between stress and smoking, there is some evidence that this may represent a promising overarching theory to guide future research. First, with respect to initiation, inbred rat strains previously shown to differ in HPA stress responses (Fischer and Lewis rats) also differ in preference for nicotine over saline, with Lewis rats (which have lower HPA responses to stress) showing greater likelihood of acquiring a preference for nicotine (Horan, Smith, Gardner, Lepore, & Ashby, 1997). Regarding maintenance, nicotine has been shown to alter functioning of both reward (mesolimbic DA and opioid peptide; Corrigall, 1999; Corrigall, Coen, Adamson, Chow, & Zhang, 2000; Watkins, Koob, & Markou, 2000) and stress response (HPA; Baron et al., 1995; Kirschbaum et al., 1993, 1994) systems.

Finally, most of the evidence regarding allostatic mechanisms has focused on withdrawal. Alterations in reward thresholds have been shown during nicotine withdrawal (Epping-Jordan et al., 1998; Watkins et al., 2000), which are believed to reflect alterations in dopaminergic systems. Although the effects of withdrawal on central CRF have not been examined, alterations along

the HPA axis (e.g., changes in peripheral corticosteroids) have been shown during withdrawal from nicotine (Frederick et al., 1998; Pickworth & Fant, 1998; Rasmussen, Kallman, & Helton, 1997); however, effects in humans are variable and not always in the expected direction (increases). Further research regarding changes in reward and stress systems during protracted withdrawal from nicotine are warranted. Again, however, mechanisms posited by this model may not be specific to nicotine and smoking.

Summary

Our review of potential mechanisms governing nicotine–affect associations reveals a multitude of diverse factors that may influence the link between smoking and stress and negative mood. Table 3 presents a summary of these models, as well as their potential applicability across the smoking initiation, maintenance, and relapse stages. In the end, there is reason to believe that mediator and moderator approaches to the problem may ultimately be more informative than direct-effect approaches, based in great part, on the inconsistent findings regarding nicotine’s effects on NA and stress. Hence, emphasis should be paid to contextual factors that may shape and modify smoking’s effects on emotional response over the developmental course of smoking behavior.

GENERAL DISCUSSION

Noting that almost all smokers attribute their smoking to its purported calming and relaxing properties, we reviewed the empirical literature in an effort to address the veracity of this claim. We observed consistent between-subjects associations between smoking status and various indices of stress and NA across the initiation and maintenance stages of smoking. Thus, on a population level, smokers generally experience more NA and stress than do nonsmokers. To a lesser extent, smoking rate appears to covary with stress and NA among those in the initiation and maintenance stage (e.g., the more reported stress and NA, the more cigarettes are smoked). However, these associations cannot speak to causality. In spite of this disclaimer, however, many have made the leap from correlation to causation, asserting that such between-subjects differences support various stress-coping, self-medication, or tension-reduction hypotheses of smoking behavior. By way of comparison, one can turn to the alcohol field, where Leonard and Blane (1999) observed,

As a field, we seem to have accepted the notion that alcohol is reinforcing because it reduces tension, and we have been undaunted in our pursuit of evidence of this basic precept, even in the face of a body of literature that is, at best, equivocal. (p. 5)

The point is that the smoking field may be on its way toward reifying a causal mechanism that is, to date, unsubstantiated. Although between-subjects, correlational data justifiably invite interpretation, only through careful laboratory and field investigation can investigators begin to understand the processes underlying the observed comorbidity.

Moving to the realm of within-subject observation of whether smokers smoke on occasions when they are experiencing stress or NA, the findings provide no answer with respect to the initiation stage, a tentative yes for those in the maintenance stage, and a clearer yes for those experiencing a smoking lapse after a period of

abstinence. At the same time, it is important to reiterate that methodological rigor must be implemented to truly establish causal links between NA and smoking. A hypothetical example may be useful here. Although ample evidence suggests that smokers are more depressed than nonsmokers, it is possible that depressed affect, per se, has no association with actual smoking behavior. Consider the individual who attributes his or her smoking to depressed mood, feels depressed prior to every cigarette smoked, and feels better subsequent to smoking. In the absence of base rate data on this individual’s depressed affect when not smoking, it is impossible to determine whether depression actually cues smoking (see Paty, Kassel, & Shiffman, 1992). Indeed, were it determined that this person generally feels depressed all the time, one could conclude that no association exists between smoking and depression (i.e., depression does not cue smoking).

The question of whether smoking and nicotine actually alleviate stress and NA yielded an equally complex picture, with some studies demonstrating genuine anxiolytic effects, others finding no effect of smoking or nicotine on mood, and several animal studies reporting anxiogenic responses. Some have interpreted such findings as suggesting that nicotine’s alleged effects on emotional regulation are simply epiphenomenal, with the exception of its ability to alleviate nicotine withdrawal (Parrott, 1999). We believe, however, that such a conclusion is premature. In fact, the variable findings summarized in this review suggest that the critical question is not whether smoking alleviates stress and NA but for whom, under what conditions, and for which stress- and affect-related outcomes does smoking in fact relieve stress or NA (Gilbert & Gilbert, 1998; Zinberg, 1984). From this perspective, we believe it imperative that future research address these questions from both a contextual and transdisciplinary framework to truly shed light on the processes subserving smoking’s effects on stress and NA.

Finally, it is important to note that the smoking stages reviewed in this article are not necessarily isomorphic with age or developmental life stage. Indeed, although the vast majority of smokers report initiating smoking as adolescents, not all of them do. Thus, in the natural ecology of smoking, the initiation stage cannot be construed as inherently restricted to adolescence, nor should one assume that all adolescent smokers are in the initiation stage; clearly, a significant proportion of adolescent smokers have already progressed to maintenance and even relapse stages (Kassel, 2000a). By implication, one limitation of our review, as well as the extant database, is that smoking stages and life span characterizations (e.g., adolescence, young adulthood, etc.) may be somewhat confounded. Future research should clearly attend to such distinctions and apply operational criteria to smoking stages that are independent of age.

A Convergence of Perspectives

Guided by a transdisciplinary approach, multiple outcomes—from social behavior to neurochemistry—should be examined and manipulated across multiple levels of analysis—from cellular to societal factors—to gain the fullest perspective on affect–smoking relationships. As such, an integrated theoretical perspective involving the interface of genetic, cellular, neural, environmental, and societal influences is clearly needed.

At the level of physiological mechanisms that may underlie nicotine’s effects on emotion, the bulk of previous research has

focused on peripheral processes (e.g., HPA axis), perhaps at the expense of fully explicating the role played by potential brain mechanisms. For example, as discussed earlier, NPY has received recent attention as a possible endogenous mediator of anxiolysis (Heilig et al., 1993). The interaction of nicotine and NPY has not been widely studied, although some reports indicate that nicotine may either increase (Li et al., 2000) or decrease (Frankish et al., 1995) NPY synthesis. Approaching the problem from a contextual perspective, a question that may warrant further study is, Under what circumstances does nicotine either increase or decrease NPY, and how is this relevant to our understanding of nicotine–affect relationships? For example, studies similar to those examining the effects of nicotine pretreatment on stress-induced DA responses (e.g., George et al., 1998, 2000) might be conducted with NPY on different strains of rats in different contexts (e.g., group vs. individual housing). Given that nicotine influences other brain systems mediating stress response, (e.g., CRF: Okuda et al., 1993; NE: Fu, Matta, James, & Sharp, 1998), these systems warrant future study as well in trying to better understand nicotine–affect associations.

At the other end of the process continuum, there is also reason to believe that societal and cultural influences play a role in shaping the outcome expectancies held by smokers for tobacco use (Shiffman, 1993). Thus, the extent to which smoking's effect on emotional response might actually vary across differing cultural milieus warrants investigation. As asserted by Pihl (1999), "Culture paints the drug-taking context with expectations of response that can also dramatically determine the actual response to the drug" (p. 253). Evidence of such culturally determined effects comes from a number of studies suggesting that emotional reactions to drugs can be shaped by cultural influences (Adamec & Pihl, 1978; Adamec, Pihl, & Leiter, 1976; Dobkin del Rios, 1973). Finally, the potential influence of both pro- and antitobacco media campaigns should be scrutinized, as they too can shape outcome expectancies, thereby modifying smoking–NA relationships. A recent study of interest found that adolescents with both high advertising receptivity and depressed moods were most vulnerable to experimentation with smoking (Tercyak, Goldman, Smith, & Audrain, 2002).

In sum, we believe that an integration and synthesis of social and biological explanations should be undertaken to fully grasp the complexity of smoking–affect associations (see Cacioppo, Bertson, Sheridan, & McClintock, 2000). Furthermore, such an approach should take developmental context into account. That is, attempts should be made to ascertain whether associations between smoking and NA and stress vary over the developmental continuum of smoking behavior. Recent epigenetic approaches to understanding substance abuse etiology among youth espouse similar sentiments and afford the opportunity to characterize the emergence of transitional phenotypes as a function of numerous reciprocal influences, including social, cultural, behavioral, neural, neuroendocrine, and genetic (Dawes et al., 2000; Wills, Sandy, & Yaeger, 2000).

Methodological Considerations

A shift in methodological perspective might also prove beneficial in examining smoking–NA interactions. Both the between- and within-subjects questions addressed by this article could be further assessed by moving out of the laboratory and into the field.

Thus, one way of thinking about between- and within-subjects questions pertaining to smoking–affect relationships is to try and answer them on a real-time basis in the smoker's real world. Ecological momentary assessment (EMA) uses handheld computers and relies on repeated assessments of subjects' momentary states in their natural environments (Shiffman & Stone, 1998). Drawing on event-contingent sampling strategies (during which subjects enter data linked to some specified behavior, e.g., smoking a cigarette) and signal-contingent sampling (where subjects enter data in response to a randomly presented, external signal), this methodology allows for determination of true antecedents and consequences of specified behaviors (Paty et al., 1992). Put simply, such an approach is uniquely suited to answer the following question: For whom, under what conditions, and for which specific stress- and affect-related outcomes does smoking relieve stress and NA (Delfino et al., 2001)?

One EMA study (Paty, 1998) reported that smoking frequently exerted genuine anxiolytic responses, reduced heightened levels of anger, and appeared to maintain feelings of calm and contentment. The EMA approach has also been used in conjunction with ambulatory measures of autonomic processes (e.g., blood pressure), thus allowing for concurrent assessment of valence and arousal components of emotion (Kamarck et al., 1998). Moreover, EMA allows for determination of the influence of context (e.g., location) on smoking–affect associations. Indeed, recent work by Tennen and colleagues (Mohr et al., 2001; Swendsen et al., 2000) have used real-time, daily diary studies to answer questions integral to the self-medication hypothesis as applied to alcohol use.

The Importance of Context

Although context often refers to the nature of the physical environment in which an organism exhibits behavior, contextual variables that affect smoking–affect interactions can exist at the level of trait differences (e.g., gender, anxiety, depression), state differences (e.g., predrug mood state), biologic determinants (e.g., dopaminergic turnover), and environmental features (e.g., presence of benign distraction). Stated differently, although the field has predominantly asked "does it or doesn't it" questions with respect to whether nicotine possesses genuine mood-modulating effects (independently of withdrawal relief), we believe it wiser to reformulate questions into ones that take context into account (Kassel, 2000b). Indeed, examination of the specific aspects of context under which drugs exert behavioral effects has long been of importance to the field of behavioral pharmacology (e.g., Barrett & Katz, 1981). Thus, principles such as baseline dependency—that the effects of drugs are inversely related to both the rate of operant responding under control conditions (rate dependency) and pre-baseline mood or cognitive functioning—have profound implications for understanding nicotine's effects on emotional response (Perkins, 1999a). Although relatively little research in both the animal and human arenas has been conducted with respect to baseline-dependency effects on nicotine–NA relationships, promising results from both within-subject and between-subjects approaches are emerging. For example, trait anxiety appears to moderate the attentionally mediated effects of nicotine on anxiety (Kassel & Unrod, 2000), whereas the stress-reducing influence of smoking has been shown to be dependent on experi-

mentally manipulated baseline stress level (Perkins, Grobe, Epstein, Caggiula, & Stiller, 1992).

As described earlier, examinations of the impact of environmental factors, such as distraction, on the smoking–affect association have also shown promise (Kassel & Shiffman, 1997; Kassel & Unrod, 2000). Exploration of contextual factors with respect to the features of specific stressors suggests that nicotine reduces NA most effectively in situations involving mild or moderate anticipatory anxiety, ambiguous stressors, or both (Gilbert, 1995; Gilbert & Welser, 1989). Conversely, there is reason to believe that nicotine would have minimal effects on emotional response to potent, direct, and proximal stimuli of sufficient hedonic value to exceed the threshold of the amygdala and other central nervous system substrates linked with affective response (Gilbert, 1995).

Finally, it is important to note that emphasis of context is equally (if not more) applicable to animal studies of nicotine–stress interactions. Because environmental and biological variables are more easily manipulated in studies of nicotine effects on animals relative to humans, such studies are rife with potential to further delineate the factors affecting nicotine’s impact on emotional response. Indeed, a recent example of such an approach was reported by Faraday et al. (1999), who found that chronic nicotine administration appeared to reduce anxiety among female, but not male, rats and that this effect was observed only among those who lived in group-housing conditions.

On the Measurement of Affect

Our review makes it apparent that the vast majority of human studies assessing nicotine’s effects on stress and NA have used verbal report as the primary measure of affect. Animal studies, on the other hand, have implemented a variety of established behavioral measures discussed earlier. The clear limitations of verbal report include potential self-report biases, lack of convergence across measures, and neglect of other critical dimensions of emotional responding (see Lang, 1995). To truly enhance understanding of nicotine’s effects on emotional response, it is imperative to incorporate multidimensional models and measures of affect (see Lang, 1968) such as those briefly reviewed earlier in this article. Such approaches allow for a more fine-grained assessment of convergent validity across response modalities and also may point to underlying biological substrates mediating any observed affect.

Correspondingly, the majority of studies reviewed in this article assessed the relationship between nicotine and emotional response from an atheoretical framework. Put simply, it is necessary to approach the study of nicotine–stress interactions from an informed theory of affect. The theories reviewed earlier in this article suggest different ways in which emotional response may be conceptualized and assessed. For example, in accordance with the two-factor model (valence and arousal) of emotion discussed earlier (Lang, 1995; Lang et al., 1990), several recent studies have used fear-potentiated startle eyeblink response as an index of affect and, in doing so, have begun to characterize the effects of various drugs on emotional response. For instance, Stritzke, Patrick, and Lang (1995) used a design wherein they presented a series of affect-laden stimuli (positive, neutral, and negative) to subjects and found that purported stress-response-dampening effects of alcohol likely involve a nonspecific attenuation of arousal reactions that was evident for positive as well as negative affective

stimuli. Thus, there was no evidence that alcohol selectively reduces negative emotional response. Diazepam, on the other hand, was found to selectively reduce fear response to NA stimuli without dampening general startle reactivity or suppressing arousal reactivity as indexed by electrodermal response (Patrick, Berthot, & Moore, 1996). The use of fear-potentiated startle response has a rich history in animal studies as well (e.g., Davis, 1986) and, as such, provides an excellent tool by which to further examine the effects of nicotine on stress and NA in both humans and animals. Moreover, marked advances have been made with respect to delineating the neural circuitry involved in the startle response (Davis & Shi, 1999; Davis, Walker, & Lee, 1999), thereby opening the door to identification of the neural substrates where nicotine exerts its effects on emotion.

On the Specificity of Affect

Our review reveals that most of the studies assessing nicotine’s effects on emotional response have actually examined nicotine’s effects on anxiety. Given the reliable association between depression and smoking, it is therefore surprising that relatively few studies have directly assessed smoking’s or nicotine’s effects on depression, or on other basic emotions for that matter. This is less true in the animal literature, where some findings suggest that nicotine can reduce behavioral symptoms of depression in rats (e.g., Tizabi et al., 1999). Approaching the smoking–affect issue from the perspective of the basic emotions approach discussed earlier in the article, one must wonder whether smoking’s effects are, indeed, specific to certain emotions and not others. This is clearly an empirical question that warrants further attention. The point is that assessment of an array of emotions is necessary to adequately characterize the effects of smoking on emotional response, in general, and on various negative affective states, in particular. As such, we think it imperative to also investigate smoking’s effects on specified positive emotions as well. Given the dearth of research examining nicotine–positive affect interactions, however, we are unable to characterize these effects at this time. In sum, a far more systematic and theory-based approach to delineation of smoking–affect relationships is needed. Such an approach would not only help clarify these complex associations but would also shed light on the biological substrates upon which nicotine exerts its effects.

The notion that smoking’s effects on arousal might be integral to its impact on emotional response also deserves future consideration. Thus, whereas the impact of nicotine on cardiovascular response and subjective stress may be independent (Perkins, Grobe, Epstein, et al., 1992), the same may not be true for its concurrent effects on arousal and depression or boredom or happiness. This is a particularly important research area within the realm of adolescent smoking. Although few data exist on the topic, it is conceivable that adolescent smokers might be particularly susceptible to the arousing properties of nicotine (Dahl, 1996) and that this process, rather than a direct effect on affective valence, might contribute to reductions in NA or increases in positive mood. Indeed, tiredness and sleep deprivation, which are frequently experienced by adolescents (Carskadon, 1990), could contribute to the subjectively positive experience of nicotine (through its effects on attention and arousal). Several studies have shown links between increased rates of smoking and getting less sleep/

tiredness in adolescents (Carskadon, 1990; Tynjala, Kannas, & Levalahti, 1997).

Can Smoking Worsen Emotional Response?

Finally, we must also be open to the possibility that smoking or nicotine, at least under certain circumstances, may manifest untoward effects on emotional response. Initial episodes of tobacco use are almost always aversive (Eissenberg & Balster, 2000). Moreover, nicotine-induced conditioned place aversion has been observed in animals following high doses of nicotine, although this may be a dose-related effect in that low doses of nicotine typically result in conditioned place preference (e.g., Risinger & Oakes, 1995). Although there is no empirical evidence suggesting that acute effects of smoking or nicotine actually worsen emotional response among regular smokers, it is conceivable that over extended periods of time, smoking may—through the emergence of a withdrawal syndrome and other as yet unspecified causal mechanisms—actually induce NA (Parrott, 1999). At the same time, even if true, this does not undermine the assertion that the acute effects of smoking and nicotine may exert genuine beneficial effects on emotional response (Kassel, 2000b). Moreover, the observation that predisposing individual differences in psychopathology (e.g., depression) mediate smoking heritability can account, at least in part, for observed differences in affective distress between smokers and nonsmokers. Although some have interpreted such between-subjects differences as reflecting the within-subject process of smoking causing stress (Parrott, 1999), such a conclusion is unwarranted on the basis of methodological grounds discussed throughout this article.

Conclusion

In the end, the relationship between cigarette smoking and stress and NA proves to be an exceedingly complex one. Indeed, the continued search for direct-effect mechanisms through which nicotine purportedly modulates emotion may prove to be a fruitless one. This is not to say that furthering the knowledge base of the underlying neural and hormonal processes associated with smoking and stress is unwarranted. On the contrary, the biologic evidence presented earlier is compelling and has greatly enhanced our understanding of some of the reinforcing neuroregulatory mechanisms likely governing nicotine administration, as well as administration of other drugs of abuse (Picciotto, 1998). However, in lieu of our findings that (a) we know very little about whether nicotine reduces stress and NA among smoking initiates; (b) nicotine yields inconsistent effects on NA and stress among regular smokers; and (c) smoking appears to have no effect on, or even worsen, NA among those in the throes of relapse, we maintain that a transdisciplinary, contextual approach to the study of stress–nicotine interactions is needed to bolster understanding of the processes governing smoking–affect relationships.

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