Nicotine Withdrawal Increases Threat-Induced Anxiety but Not Fear: Neuroadaptation in Human Addiction

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Background: Stress response neuroadaptation has been repeatedly implicated in animal addiction models for many drugs, including nicotine. Programmatic laboratory research that examines the stress response of nicotine-deprived humans is necessary to confirm that stress neuroadaptations observed in animal models generalize to humans.

Methods: Two experiments tested the prediction that nicotine deprivation selectively increases startle response associated with anxiety during unpredictable threat but not fear during imminent, predictable threat. Dependent smokers ($n = 117$) were randomly assigned to 24-hour nicotine-deprived or nondeprived groups and participated in one of two experiments wherein electric shock was administered either unpredictably (noncontingent shock; Experiment 1) or predictably (cue-contingent shock; Experiment 2).

Results: Nicotine deprivation increased overall startle response in Experiment 1, which involved unpredictable administration of shock. Age of first cigarette and years of daily smoking were significant moderators of this deprivation effect. Self-reported withdrawal symptoms also predicted startle response during unpredictable shock. In contrast, nicotine deprivation did not alter overall or fear-potentiated startle in Experiment 2, which involved predictable administration of shock.

Conclusions: These results provide evidence that startle response during unpredictable threat may be a biomarker of stress neuroadaptations among smokers in nicotine withdrawal. Contrast of results across unpredictable versus predictable shock experiments provides preliminary evidence that these stress neuroadaptations manifest selectively as anxiety during unpredictable threat rather than in every stressful context. Individual differences in unpredictable threat startle response associated with withdrawal symptoms, age of first cigarette, and years daily smoking link this laboratory biomarker to clinically relevant indexes of addiction risk and relapse.

Key Words: Addiction, anxiety, fear, nicotine withdrawal, startle response, stress neuroadaptation

Classic and contemporary theories of addiction indicate that drug addiction results from compensatory changes in the neural circuitry involved in emotion and motivation (1,2). Many of these theories specifically implicate neuroadaptation in the stress response as a critical mechanism in the development of addiction across drugs, including nicotine (3–5). Repeated homeostatic adjustments in the brain's stress systems during periods of drug use eventually lead to chronic compensatory adaptations in the structures involved in emotional response and its regulation. These adaptations persist beyond periods of acute use and result in dysregulated negative affect (e.g., increased anxiety) on cessation of use (3).

Animal models have provided substantial evidence to support this stress neuroadaptation thesis (3–4). Reliable report of increased negative affect during withdrawal from most common addictive drugs (e.g., nicotine, alcohol, opiates, cocaine) provides preliminary support for this thesis in humans (6). However, programmatic laboratory research that examines the stress response of drug-deprived humans is necessary to confirm that stress neuroadaptations observed in animal models generalize to human addiction etiology. This program of research will be particularly informative if laboratory assays and dependent measures are selected to facilitate animal–human translation and to identify precise biobehavioral markers of the putative stress neuroadaptations that result from chronic drug use. Following these recommendations, the experiments described in this report examined affective response during stress exposure among nicotine-dependent smokers during withdrawal following 24 hours of nicotine deprivation. We examined startle potentiation using procedures that have been employed with rodents, nonhuman primates, and humans to probe the neurobiological substrates of negative affective response and pharmacological effects on these processes during threat (7–11). In addition, we manipulated threat contingencies following procedures that have been recently developed to parse fear and anxiety during stress precisely (12).

The startle response provides an attractive, noninvasive methodology for examining the effects of drug administration and deprivation on affective response during stress in both animals and humans. The startle response to an abrupt, intense stimulus (e.g., loud noise) increases above baseline when elicited in the presence of a cue that has been paired contingently with an aversive unconditioned stimulus (7). This effect is referred to as fear-potentiated startle, and substantial research with rodents has confirmed that projections from the central nucleus of the amygdala (CeA) to the primary startle circuit (cochlear root neurons to pontis caudalis to facial motor neurons and spinal cord) are responsible for this startle potentiation (7).

Research has identified other manipulations that also potentiate the startle response in animals and humans. Corticotropin-releasing factor (CRF) and bright light potentiate the startle response in rats (13–15). In humans, exposure to darkness (16) and unpredictable electric shock (11,17) increase startle response magnitude. However, there are important differences in the nature of the response produced by CRF, light–darkness, and noncontingent (unpredictable) shocks versus cue-contingent electric shock administration. Specifically, cue-contingent administration of electric shock produces phasic fear-potentiated startle only during the punctate cues that predict imminent shock administration (7,9,12). In contrast, CRF, light–darkness, and unpredictable shock administration produce more sustained potentiation of the startle reflex. More-

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over, Davis and colleagues (18) have demonstrated elegant double dissociations in the neural substrates underlying startle potentiation across these two classes of manipulations in rodents. Specifically, lesions of the central nucleus of the amygdala (CeA) abolished fear-potentiated startle to cued shock but not potentiation of startle to CRF and bright light exposure. In contrast, lesions of the bed nucleus of the stria terminalis (BNST) abolished startle potentiation to CRF and bright light exposure but not fear-potentiated startle during cued shock.

Given the nature of the eliciting stimuli and the time course of the response across these two categories of manipulations, researchers have offered these manipulations as laboratory models of fear vs. anxiety (12). Specifically, contingent cue-electric shock pairings involve simple, punctate stimuli that are predictive of imminent aversive stimulation. The phasic fear potentiation of startle during cues that predict shock is proposed to model the fear response. In contrast, noncontingent, uncued, shock, light–darkness, and CRF involve more complex, diffuse contextual cues that are more static or of longer duration and provide little information about when aversive stimulation will occur. Sustained startle response potentiation in these manipulations is proposed to model anxiety.

Preliminary research that has used the startle response to examine the consequences of nicotine deprivation has failed to detect changes in affective response during brief unpleasant events and punctate, cued threats. For example, nicotine deprivation does not increase startle potentiation observed during brief (6 sec) presentation of unpleasant relative to neutral images (19,20). With respect to potent, punctate threat, Hogle and Curtin (10) reported that 24-hour nicotine-deprived smokers did not display increased startle potentiation during anticipation of imminent, cued administration of electric shock. Thus, nicotine deprivation following chronic use does not appear to alter phasic fear potentiation of the startle reflex. However, deprivation did increase startle potentiation in the "recovery period" following the termination of the specific threat in this same experiment. This suggests that the deprived smokers may have experienced increased anxiety associated with future, more distal threats (during subsequent shock cues) leading to prolonged negative affect during the recovery period between threats. However, alternative explanations (e.g., deficient emotion regulation) of these findings are possible. The two experiments described in this report were designed specifically to test the prediction that nicotine deprivation among dependent smokers selectively increases startle response associated with anxiety during unpredictable threat (Experiment 1) but not fear during imminent cued threat (Experiment 2) or more generally in the absence of any threat (i.e., neutral baseline conditions across both experiments).

Methods and Materials

Participants

One hundred seventeen chronic smokers aged 18 or older completed one of two separate experiments (Table 1 provides description of participant characteristics). All participants reported ≥10 cigarettes/day ≥1 year, Fagerström Test for Nicotine Dependence (FTND) (21) score ≥4, and expired air carbon monoxide (CO) level ≥10 ppm during screening session. Startle nonresponders (resting startle response during screening session <4 μV) were excluded. All participants were compensated $20/hour for time spent in the laboratory. Deprived smokers were provided a $20 bonus for abstaining from tobacco products for 24 hours. See top section of Table 1 for summary of participant demographics and smoking-relevant individual differences for each experiment.

General Procedures

The general procedures were the same for both experiments. All procedures were approved by the University of Wisconsin Institutional Review Board.

Screening Session. Inclusion–exclusion criteria, demographics, smoking-relevant individual differences, and resting startle response were assessed during a laboratory screening session. This included self-report measures of nicotine dependence (FTND; Wisconsin Smoking Dependence Motives) (21,22). Resting startle response to nine acoustic probes was measured to assess individual differences in startle response before deprivation group assignment. Eligible participants were randomly assigned to one of two

Table 1. Descriptive Statistics for Individual Difference and Manipulation Check Measures by Deprivation Group for Each Experiment

	Experiment 1: Unpredictable Shocks			Experiment 2: Predictable Shocks		
	Nondeprived	Deprived	*d*	Nondeprived	Deprived	*d*
Total *N*	31	29		27	30	
Female *N*	13	16		15	14	
Age	39.9 (11.5)	35.2 (15.1)	−.35	38.0 (12.8)	34.5 (11.9)	−.28
Screening CO Level	26.9 (14.1)	24.9 (13.1)	−.15	26.8 (16.0)	26.0 (11.7)	−.05
Cigarettes per Day	21.2 (8.8)	18.6 (7.5)	−.31	18.0 (7.8)	16.0 (4.3)	−.32
Age of First Cigarette	14.0 (3.0)	14.0 (2.5)	.02	13.8 (4.3)	15.0 (6.5)	.23
Age of Smoking Daily	15.7 (2.4)	16.5 (2.9)	.30	16.4 (3.2)	17.3 (5.5)	.21
Years Smoking Daily	22.8 (11.0)	16.6 (13.2)	−.51	18.2 (12.5)	16.5 (12.5)	−.14
FTND	6.1 (1.6)	5.8 (1.7)	−.21	6.3 (1.7)	5.9 (1.5)	−.28
WISDM	52.2 (16.7)	56.2 (14.5)	−.25	53.5 (14.2)	52.3 (15.3)	−.08
Experiment CO Level	28.3 (13.2)[c]	5.6 (5.2)[c]	−2.26	29.0 (19.8)[c]	5.7 (4.1)[c]	−1.64
WSWS	14.4 (4.8)[a]	17.4 (4.3)[a]	.66	13.2 (2)[a]	15.9 (3.6)[a]	.55

Means (SDs) are presented for each measure by deprivation group for each experiment. Cohen's *d* is also reported to document observed effect size. Significant Deprivation Group differences are indicated in each experiment.

CO, carbon monoxide level measured in parts per million during screening and experimental sessions; FTND, Fagerström Test for Nicotine Dependence (21) (Cronbach's α = .61); WISDM, Wisconsin Inventory for Smoking Dependence Motives (22) (Cronbach's α = .96); WSWS, Wisconsin Smoking Withdrawal Scale (23) (Cronbach's α = .93).

[a] $p < .05$.

[b] $p < .001$.

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