Psychopharmacology (1999) 141 : 11–15

ORIGINAL INVESTIGATION

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Smoking withdrawal, nicotine dependence and prepulse inhibition of the acoustic startle reflex

Received: 26 November 1997/Final version: 8 June 1998

Abstract The present study examined the relationship between nicotine dependence as measured by the Fagerstrom Tolerance Questionnaire (FTQ) and prepulse inhibition (PPI) of the acoustic startle reflex measured after overnight smoking withdrawal in a non-clinical population of male smokers with no history of psychiatric disorders or drug/alcohol abuse. It was found that smokers who scored high (>median) on the FTQ showed significantly less PPI as compared to those scoring low (<median) on this scale. This finding further supports a role for nicotine in modulation of PPI, as has previously been found in rats and also in human beings.

Key words Prepulse inhibition · Acoustic startle reflex · Smoking withdrawal · Nicotine dependence

Introduction

Prepulse inhibition (PPI) of the startle reflex refers to a reduction in magnitude of the startle reflex when a strong startle-eliciting stimulus (pulse) is preceded 30–100 ms by a weak prestimulus (prepulse) which on its own does not elicit a measurable response (Graham 1975). There are a number of studies showing that PPI of the acoustic startle is deficient in schizophrenia (Braff et al. 1978, 1992; Grillon et al. 1992; Bolino et al. 1994; Hamm et al. 1995) and related disorders (Cadenhead et al. 1993). Drugs which reduce (e.g. amphetamine, apomorphine; for reviews, see Swerdlow et al. 1992, 1994; Campeau and Davis 1995) and enhance (e.g. clozapine, haloperidol; Swerdlow and Geyer 1993; Hoffman and Donovan 1994) PPI have psychotic and antipsychotic properties, respectively, in humans, suggesting the potential usefulness of PPI as a tool to screen antipsychotic drugs (Varty and Higgins 1995). However, there are also reports indicating deficient PPI in disorders other than schizophrenia, for example, in patients with post-traumatic stress (Grillon et al. 1996) and obsessive-compulsive (Swerdlow et al. 1993) disorders, as well as the involvement of other than dopaminergic neurochemical mechanisms in PPI, for example, acetylcholine (Koch et al. 1993; Wu et al. 1993; Curzon et al. 1994), glutamate (Hoffman et al. 1993), GABA (Kodsi and Swerdlow 1995) and serotonin (Sipes and Geyer 1994, 1995a,b; Varty and Higgins 1995).

Nicotine is one of the several pharmacological agents that modulate PPI. Nicotine has been found to enhance PPI in both animals (Acri et al. 1994; Curzon et al. 1994) and human beings (Kumari et al. 1996, 1997a), though studies have not yet identified the mechanism through which this influence is exerted. We earlier reported that nicotine administration via cigarette smoking to a group of overnight smoking-deprived smokers increased PPI (Kumari et al. 1996), a finding confirmed by J. Feldon (personal communication). More recently, we (Kumari et al. 1997b) observed that nicotine (12 μg/kg) administered subcutaneously to a group of male non-smokers also enhanced PPI as compared to that observed under saline administration.

In this report, we examine whether nicotine dependence as assessed by the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom 1978) has a modulatory influence on PPI of the acoustic startle measured after overnight smoking withdrawal in healthy male smokers. On the basis of our initial observation of an

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enhancement of PPI by smoking one cigarette after overnight smoking withdrawal, we postulated that smokers who are heavily dependent on nicotine would show less PPI as compared to smokers who are not so dependent on nicotine under smoking withdrawal.

Materials and methods

Subjects

Thirty-two right-handed (19–45 years old; mean age: 28.45, SD = 6.62) healthy male smokers, who had been smoking ten or more cigarettes daily for at least two years (mean past duration of smoking: 11.67 years, SD = 5.81), were recruited from responses to advertisements and from referrals by other subjects. The mean FTQ score for the overall sample was 5.45 (SD = 2.06; median = 6).

All subjects underwent a semi-structured interview to ensure that they were free of mental disorders, any type of medication, and drug abuse (ascertained by urine toxicology screen). All subjects, who participated in the study signed a consent form approved by the Ethical Committee at the Institute of Psychiatry, London. Subjects received £15 each for their participation.

Startle response measurement

Subjects were initially screened using an audiometer (Kamplex, AS7) at 40 dB [A] (1000 Hz) for intact auditory abilities. No subject was excluded on account of hearing deficit.

A commercial computerized human startle response monitoring system (Mark I, SR-Lab, San Diego, Calif., USA) was used to deliver acoustic startle stimuli, to record and score the electromyographic (EMG) activity for 250 ms starting from the onset of the acoustic startle stimulus. Acoustic startle stimuli were presented binaurally through headphones (Telephonics, TDH-39P). The experimental session was the same as reported by Kumari et al. (1996). Briefly stated, the pulse stimulus was a 40-ms presentation of 116-dB (A) white noise and the prepulse stimulus a 20-ms presentation of 85-dB (A) white noise, both over 70-dB (A) background noise. An initial pulse-alone trial was followed by 72 trials in six blocks of 12 trials each. Each block had three pulse-alone trials, three prepulse trials with a 30-ms prepulse-to-pulse interval, three prepulse trials with a 60-ms prepulse-to-pulse interval, and three prepulse trials with a 120-ms prepulse-to-pulse interval, presented to subjects in a pseudorandom order with a mean inter-trial interval of 15 s (range 9–23 s). Each experimental session began with a 5-min acclimatisation period consisting of 70-db (A) continuous white noise, and took approximately 23 min in all.

EMG recordings were taken with subjects sitting comfortably in a sound attenuated moderately lit laboratory. Recording and scoring criteria were identical to those reported in previous studies (Kumari et al. 1996, 1997a,b). EMG activity of the orbicularis oculi muscle of the right eye was recorded with two Ag/Agcl 6 mm electrodes, filled with Dracard (SLE, Croydon, UK) electrolyte paste. The ground electrode was placed behind the right ear over the mastoid. The amplifier gain control was kept constant (on point 3) for all subjects. The startle system continuously recorded the EMG activity for 250 ms (sampling rate 1 ms) starting with the onset of the acoustic stimulus. Latency to response onset (in ms) was defined by a shift of 6 digital units from the baseline value occurring within 18–100 ms after the stimulus. The latency to response peak (in ms) was determined as the point of maximal amplitude that occurred within 150 ms from the acoustic stimulus. Responses were rejected if the onset and peak latencies differed by more than 95 ms or when the baseline values shifted by more than 90 units.

Measurement of nicotine dependence

For the nicotine dependence measure, the sample was divided by median split on the FTQ into low (<median; $n = 14$) and high (>median; $n = 12$) nicotine dependent groups. Subjects having the median FTQ score (score 6) were excluded ($n = 5$). The mean FTQ score for the high scoring group was 7.50 (SD = 0.67) and for the low scoring group 3.50 (SD = 1.16). Three subjects (out of 12) of the high nicotine dependent group smoked 15 or more cigarettes daily, and nine subjects smoked 20 or more cigarettes daily, with all subjects smoking the first cigarette of the day within 30 min of awakening. Eleven subjects (out of 14) assigned to the low nicotine dependent group smoked between ten and 15 cigarettes daily and three subjects smoked 20 or more cigarettes daily. Only two subjects of the low nicotine dependent group reported smoking the first cigarette of the day within 30 min of awakening.

Experimental procedure

Subjects were told that the study was to investigate the influence of smoking habit on reactivity to loud noises, but no specific instructions were given to attend to or ignore the stimuli. They were told "You are going to hear a number of auditory clicks, some of which may make you blink. Please keep your eyes open during this experiment which would last about 25 minutes." Subjects were not required to make any voluntary responses.

They were requested to refrain from smoking for at least 12 h prior to reporting for the testing session. Non-smoking compliance was checked upon arrival using an expired air carbon monoxide (ECO) monitor (Bedfont Technical Instruments EC 50). Subjects with ECO levels over 12 ppm were not tested ($n = 1$). Subjects were then taken to the laboratory and startle testing commenced. All subjects were tested in the morning between 9.00 and 11.00 a.m. Subjects completed the FTQ after the end of the startle experiment.

Statistical analyses

All analyses were performed by SPSS windows (version 6). PPI was computed as $(a-b/a) \times 100$, where "a" = pulse-alone and "b" = amplitude over prepulse trials. Firstly, the influence of nicotine dependence on amplitude and habituation of the startle was assessed by submitting the data over pulse-alone trials to a 6 (Block) × 2 (Group: low and high nicotine dependent groups) multivariate analyses of variance (MANOVA) with repeated measures over blocks. Next, to examine the role of nicotine dependence in PPI, the data were subjected to a 3 (Trial type: PPI on 30-ms, 60-ms and 120-ms prepulse trials) × 2 (Group) MANOVA. Finally, the latencies to response onset and peak were analyzed by 4 (Trial type: Pulse-alone, 30-ms, 60-ms and 120-ms prepulse trials) × 2 (Group) MANOVAs.

Results

There was a strong habituation with repeated presentation of pulse-alone trials over the entire session (Block: $F5,20 = 4.84$, $P < 0.01$; Lin $t = 4.67$, $P < 0.001$), but there was no significant influence of nicotine dependence on either the amplitude or habituation of the startle response (Fs > 1) (see Table 1 for the mean values).

Nicotine dependence had a significant effect on PPI (Group: $F1,24 = 6.96$, $P = 0.01$), indicating that the

Table 1 Mean (SEM) response amplitudes (in analogue to digit units, each unit = 1.22 mv) over the six blocks of three pulse-alone trials each for the low and high nicotine dependent groups

	Low nicotine dependent	High nicotine dependent
Block 1	228.55 (27.86)	270.01 (41.02)
Block 2	212.24 (28.43)	255.11 (42.57)
Block 3	173.57 (25.56)	234.54 (41.39)
Block 4	170.64 (26.96)	214.25 (40.71)
Block 5	160.64 (32.79)	187.40 (37.57)
Block 6	160.43 (28.88)	176.42 (34.60)

high FTQ scoring (i.e. highly nicotine dependent) smokers showed less PPI than the low FTQ scoring smokers (see Fig. 1). There was a linear increase in PPI from 30-ms, through 60-ms to 120-ms prepulse trials (Trial type: $F2,23 = 22.26$, $P < 0.001$; Lin $t = 6.53$, $P < 0.001$), but there was no Group × Trial type interaction ($F > 1$), indicating a similar effect of nicotine dependence on PPI at all three prepulse intervals.

There were only main effects of Trial type for the latencies to response onset ($F3,24 = 16.22$, $P < 0.001$) and response peak ($F3,24 = 31.70$, $P < 0.001$) (see Table 2 for the means for the low and the high FTQ scoring groups). There were no other significant effects (Fs < 2).

Discussion

This study showed that smokers who were highly dependent on nicotine, as assessed by the FTQ, showed less PPI under smoking withdrawal as compared to those who were not so heavily dependent. This finding provides further evidence that nicotine plays a role in the regulation of human PPI (Kumari et al. 1996, 1997a,b; J. Feldon, personal communication), an observation in line with current animal literature (Acri et al. 1994; Curzon et al. 1994).

Nicotine dependence had no influence on other startle measures (i.e. amplitude, habituation and the latencies to response onset and peak), indicating that the above finding was neither confounded by nor secondary to changes in other startle measures. In rats, an abrupt cessation of nicotine treatment results in increased startle reactivity (Helton et al. 1993). We did not, however, test smokers who were not under withdrawal and therefore are unable to explore directly whether smoking withdrawal increases startle reactivity in smokers.

There is some evidence in the rat that stress can affect PPI (Leitner 1986). It is possible that highly nicotine dependent smokers suffered more severe withdrawal symptoms (Pomerleau et al. 1983; Hatsukami et al. 1985) after overnight smoking withdrawal which led to lower levels of PPI in this group, as compared to that observed in those who were only lightly dependent on nicotine. It should, however, be noted that the FTQ scores correlate consistently positively with other potential measures of nicotine dependence, for example, plasma nicotine and cotinine levels, but evidence for the correlation between the FTQ scores and withdrawal symptoms is rather weak (see review, Fagerstrom and Schneider 1989).

Table 2 Mean (SEM) latencies to response onset (ms) and response peak (ms) for pulse-alone trials and for trials with 30-ms, 60-ms and 120-ms prepulse-to-pulse intervals for the low and the high nicotine dependent groups

	Pulse-alone	30-ms	60-ms	120-ms
Latency to onset				
Nicotine dependence				
Low	36.09	31.86	35.39	37.76
	(1.34)	(1.36)	(2.01)	(2.08)
High	34.99	31.35	35.46	36.39
	(1.80)	(2.28)	(2.24)	(2.57)
Latency to peak				
Nicotine dependence				
Low	57.86	49.71	54.08	52.66
	(0.65)	(1.30)	(1.15)	(1.62)
High	56.71	49.54	52.66	53.12
	(1.39)	(1.38)	(1.62)	(1.69)

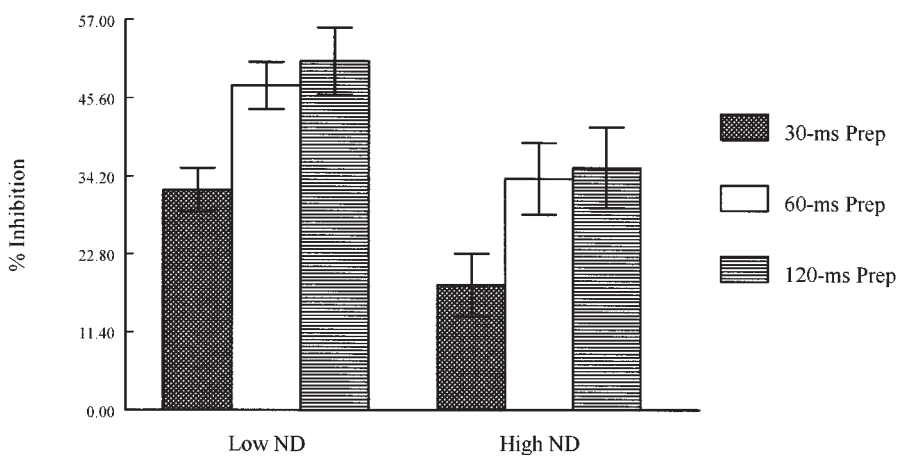

Fig. 1 Mean (percent) prepulse inhibition (error bars display ±1 SEM) of the startle reflex response by prepulse (*Prep*) trials with 30-ms, 60-ms and 120-ms prepulse-to-pulse intervals for the low and high nicotine dependent (*ND*) groups

The present study was designed primarily to look at the role of nicotine dependence in PPI under smoking withdrawal. Further systematic investigation is required to assess whether there is a direct relationship between smoking withdrawal induced stress and/or attentional deficits and levels of PPI. Since average prepulse identification has been found to be significantly higher on trials during which startle is inhibited, compared to trials during which it is not (Norris and Blumenthal 1996), asking subjects to identify prepulse trials and then examining the relationship, if any, between the correct identification of prepulse trials and withdrawal severity may help to establish the mechanism for the influence of nicotine dependence on PPI.

Another possibility is that heavy nicotine intake by smokers, at least in part, may reflect a self-attempt to restore some trait-like cognitive deficits, for example, those indexed by deficient PPI of the startle reflex. Smoking at a desired level presumably masks the deficits that are present prior to taking up the smoking habit. This, if true, would suggest no difference between low and highly nicotine dependent groups for PPI measured after optimal/self-desired levels of smoking intake. Future studies could extend the present study to test this possibility.

Acknowledgements This research was supported by British American Tobacco. We thank Ms. L. Poon for her excellent assistance in recruiting and screening the subjects.

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