Psychopharmacology (1994) 116:93–97

Psychopharmacology

Acute pharmacodynamic tolerance to the subjective effects of cigarette smoking

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Received: 16 July 1993 / Final version: 17 December 1993

Abstract. A brief feeling state questionnaire was completed before and after each cigarette, over a day of smoking. Feelings of stress/anxiety demonstrated a pattern of repetitive vacilation over the day, with high stress before smoking, reduced stress after smoking, and stress levels increasing again between cigarettes. There was no evidence of acute pharmacodynamic tolerance, with cigarettes leading to altered feelings of anxiety/stress over the whole day of smoking. Self-rated feelings of arousal also demonstrated a pattern of vacilation over the day, with low arousal pre-smoking, increased arousal post-smoking, but arousal levels reducing again between cigarettes. The ANOVA drug × time interaction was significant, with the greatest arousal change following the first cigarette of the day. However, later cigarettes led to similar amounts of arousal change over the rest of day, thus questioning whether acute pharmacodynamic tolerance was occurring. Instead, the heightened arousal response to the first cigarette of the day may reflect the influence of two other factors. Firstly, overnight deprivation, with the first cigarette of the day leading to the greatest increase in plasma nicotine. Secondly, low early-morning arousal with its associated potential for increased arousal. Overall, therefore, there was little indication of acute pharmacodynamic tolerance to the subjective effects of nicotine. Cigarettes were associated with altered feelings of stress and arousal, over the whole day of smoking.

Key words: Nicotine – Cigarette – Smoking – Tolerance – Pharmacodynamics – Arousal – Stress – Anxiety

Cigarette smoking has been shown to affect a variety of psychological functions: EEG indices of alertness, sustained attention, feelings of stress and anxiety (Surgeon General 1988; Warburton et al. 1988; Church 1989; Gilbert and Wesler 1989; Russell 1989; Wesnes and Parrott 1992). However, much of the data on these psychological changes has come from acute single-dose studies, and there is comparatively little information on the repeated-dose effects of nicotine. In particular, there is little systematic data on whether the psychological effects of nicotine are subject to acute or chronic tolerance. West (1990, pp. 216–217) noted that studies investigating tolerance to the subjective effects of nicotine/smoking were clearly needed. The Surgeon General (1988, pp. 44–55) also commented upon the paucity of studies in this area. However, Russell (1989) suggested that regular smokers demonstrate acute tolerance, with the first cigarette of the day having clear psychological effects, but later cigarettes producing few psychological changes. In contrast, Warburton et al. (1988) found no evidence for acute tolerance, and proposed instead that the subjective/mood effects of nicotine should continue throughout the smoking day.

The present study comprised one of a series of investigations into the psychological effects of cigarette smoking (O'Neill and Parrott 1992; Parrott 1992, 1993; Parrott and Joyce 1993). Feelings of stress and arousal were monitored over a day of normal smoking, in subjects categorised as sedative or stimulant (using the Smoking Motivation Questionnaire; West and Russell 1985). The main findings from this study are being published elsewhere (Parrott 1994). This report is concerned with the question of acute tolerance. Self-rated feeling states were assessed before and after each cigarette, over the whole day of smoking. Acute tolerance would be evident if the subjective effects of cigarettes reduced significantly over time. In contrast, if all cigarettes over the day were associated with similar amounts of feeling state change, then tolerance would not be in evidence. However, two confounding factors may influence the above equation: differences in plasma nicotine concentration, and differences in subjective state, prior to each cigarette. These factors vary over the day, and may influence the degree of psychological change found after each cigarette.

Material and methods

Subjects. Unpaid volunteers ($n = 105$) from the staff and students at the University of East London: 65 female and 40 male, in the age range 18–75 years (mean: 30.4), smoking 4–28 cigarettes on the test day (mean: 12.6). Further subject details are shown in the paper by Parrott (1994).

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Assessment measures. The Smoking Motivation Questionnaire (SMQ; West and Russell 1985) was used to categorise subjects into sedative and stimulant subgroups (see below). The self-rating mood questionnaire was derived from Mackay et al. (1978). The first two questions (below) loaded on the stress factor, while the final two questions loaded on the arousal factor:

Tense strongly, slightly, neither, slightly, strongly, Relaxed
Nervous strongly, slightly, neither, slightly, strongly, Calm
Energetic strongly, slightly, neither, slightly, strongly, Tired
Alert strongly, slightly, neither, slightly, strongly, Drowsy

Each question was scored from 5 to 1. Overall stress and arousal scores therefore ranged from 2 (low) to 10 (high). This questionnaire was completed immediately before and after each cigarette, over a day of normal smoking. Since smokers consume different numbers of cigarettes, the data were split into four time blocks. The score for the first cigarette of the day represented block 1, while the last cigarette of the day represented block 4. The remaining cigarettes were split into two consecutive halves, with the means of each half representing blocks 2 and 3. Each subject smoked his or her normal brand of cigarette, on an alcohol-free day (Parrott 1993, 1994).

Method of analysis. The stress data were analysed by split-plot ANOVA with three factors: sedative subgroup (five subgroups with the following SMQ sedative subscale scores: 0–2, 3–4, 5–6, 7–8, 9), drug (pre/post-cigarette), and time (four time blocks). The arousal data were analysed by similar split-plot ANOVA with three factors: stimulant subgroup (four subgroups with the following SMQ stimulant subscale scores: 0–2, 3–4, 5–6, 7–9), drug (pre/post-cigarette), and time (four time blocks). Note: four stimulant groups were used instead of five, because relatively few subjects generated near-maximum stimulant subscale scores (Parrott 1994).

Results

Feelings of stress were significantly affected by drug ($P < 0.001$) and time ($P < 0.001$). Stress was higher pre-smoking than post-smoking, and reduced gradually over the day (Tables 1,3). The drug × time interaction was non-significant, showing that the effect of smoking upon stress

Table 1. Pre-cigarette and post-cigarette stress values for the five SMQ sedative subgroups

		Time block 1			Time block 2			Time block 3			Time block 4		
SMQ Score	sedative *n*	Pre smoke	Post smoke	Pre-post diff	Pre smoke	Post smoke	Pre-post diff	Pre smoke	Post smoke	Pre-post diff	Pre smoke	Post smoke	Pre-post diff
0–2	6	5.0	4.8	− 0.2	5.3	5.3	0.0	4.7	4.7	0.0	3.8	4.5	+ 0.7
3–4	23	5.9	5.1	− 0.8	5.2	4.7	− 0.5	5.4	4.9	− 0.5	5.0	4.4	− 0.6
5–6	17	5.4	4.8	− 0.6	5.6	4.7	− 0.9	5.7	4.4	− 1.3	4.2	4.1	− 0.1
7–8	30	5.9	4.7	− 1.2	5.9	4.9	− 1.0	5.0	4.5	− 0.5	4.2	3.4	− 0.8
9	29	6.3	4.8	− 1.5	5.9	4.6	− 1.3	5.7	4.5	− 1.2	4.9	4.0	− 0.9
All	105	5.9	4.8	− 1.1	5.6	4.8	− 0.8	5.3	4.6	− 0.7	4.5	4.0	− 0.5

High score = high stress; low score = low stress; minus difference score = reduced stress post-drug

Table 2. Arousal values pre-smoking and post-smoking, for the four SMQ stimulant subgroups

		Time block 1			Time block 2			Time block 3			Time block 4		
SMQ Score	stimulant *n*	Pre smoke	Post smoke	Pre-post diff	Pre smoke	Post smoke	Pre-post diff	Pre smoke	Post smoke	Pre-post diff	Pre smoke	Post smoke	Pre-post diff
0–2	34	5.9	6.1	+ 0.2	6.6	6.7	+ 0.1	6.2	6.4	+ 0.2	4.9	5.4	+ 0.5
3–4	32	5.7	6.4	+ 0.7	6.3	6.6	+ 0.3	5.8	6.0	+ 0.2	4.2	4.4	+ 0.2
5–6	28	4.8	6.0	+ 1.2	6.0	6.4	+ 0.4	5.7	6.3	+ 0.6	4.1	4.7	+ 0.6
7–9	11	4.8	6.6	+ 1.8	6.1	6.8	+ 0.7	5.4	6.5	+ 1.1	3.8	4.8	+ 1.0
All	105	5.4	6.2	+ 0.8	6.3	6.6	+ 0.3	5.9	6.3	+ 0.4	4.4	4.9	+ 0.5

High score = high arousal; low score = low arousal; plus difference score = increased arousal post-drug

Table 3. Summary of ANOVA findings (note: five sedative subgroups for stress data: four stimulant subgroups for arousal data

	Stress			Arousal		
	F-value	df	Significance	F-value	df	Significance
Subject group	0.48	4.100		1.42	3.101	
Drug	23.56	1.100	0.001	32.77	1.101	0.001
Time	9.52	3.300	0.001	26.06	3.303	0.001
Group × drug	2.09	4.100	0.10	3.06	3.101	0.05
Group × time	0.73	12.300		0.55	9.303	
Drug × time	1.88	3.300		2.90	3.303	0.05
Group × drug × time	0.90	12.300		0.68	9.303	

did not change over the day. The group × drug interaction was borderline ($P = 0.087$). This is discussed elsewhere (Parrott 1994), where the monotonic function across subgroups is shown to be significant (high SMQ sedative subgroups reported the greatest stress modulation, while low sedative subgroups noted minimal stress change). None of the other ANOVA effects was significant.

Self-rated feelings of arousal were significantly affected by drug ($P < 0.001$), and time ($P < 0.001$). Arousal was higher post-smoking than pre-smoking, while the pattern of change over time followed an inverted-U function (Tables 2,3). The drug × time interaction was significant ($P < 0.05$), with the greatest arousal increase following the first cigarette of the day (+ 0.8), and later cigarettes associated with lower amounts of arousal modulation (+ 0.3, + 0.4, and + 0.5, respectively; Table 2). The significant group × drug interaction ($P < 0.05$) reflected the greater arousal modulation reported by high SMQ stimulant smokers (Table 2; see Parrott 1994, for a detailed analysis).

Discussion

"Tolerance is defined as when, after repeated doses, a given dose of a drug produces less effect" (Benowitz 1990, p. 186). If tolerance develops within one or two doses, it is referred to as acute tolerance or tachyphylaxis. When it develops after more prolonged use, it is called acquired or chronic tolerance (Surgeon General 1988). The importance of acute and chronic nicotine tolerance has been previously discussed (Jarvik and Hatsukami 1989; Russell 1989; Surgeon General 1988; Benowitz 1990; West 1990). West (1990, p. 216–217) briefly reviewed current evidence on nicotine tolerance, and concluded that while some functions demonstrated acute tolerance (e.g. tachycardia), others did not (e.g. peripheral vasoconstriction). West (1990, p. 217) also noted: "Important from the point of view of understanding psychological dependence is tolerance to the subjective effects of nicotine. Very little systematic data has been collected to address the issue of acute and chronic tolerance to nicotine's subjective effects". The Surgeon General (1988) similarly noted the paucity of empirical studies in this area. However, some limited evidence has been collected. Warburton et al. (1988) monitored self-rated feelings states, with two cigarettes smoked 30 min apart. Subjects reported becoming: "Calmer, more tranquil, more sociable, more friendly, more contented, more relaxed, and happier", with each cigarette. Furthermore: "The baseline for the second cigarette, was lower than the peak at the end of the first cigarette but had not returned to pre-smoking levels. During smoking the second cigarette, the mood changes increased until they were above the level that was achieved at the end of the first cigarette". It was concluded that there was no evidence of acute tolerance; instead it was predicted that mood states would continue to improve throughout the smoking day (Warburton et al., 1988, p. 361). In contrast, Rosenberg et al. (1980, p. 521) claimed that the subjective effects of nicotine demonstrated "complete tolerance ", and were found only after the first nicotine challenge of the day. However, the empirical basis for this statement was very unclear. The subjective assessment points in that study did not clearly correspond to pre-nicotine or post-nicotine administration times. Also, no data were presented, nor was any statistical evidence offered. Yet this study has been quoted as evidence for acute pharmacodynamic tolerance (e.g. Surgeon General, 1988, p. 48). In a similar vein, Russell (1989, p. 300) has written: "Due to accumulation of nicotine and other pharmacokinetic factors, for most of the day and much of the night, regular smokers have high levels of acute tolerance to nicotine... This explains why heavy smokers experience no subjective effects from a cigarette smoked during the course of a normal smoking day". However, it should be noted that Russell's conclusions related (partially) to subjective feelings of nausea and lightheadedness following smoking.

The present study demonstrated that stress modulation occurred over the whole day of smoking (Table 1). The general pattern was of vacillating stress, with lower stress post-smoking than pre-smoking, but stress values increasing between cigarettes. This is discussed more fully elsewhere (Parrott 1994), where the positive mood changes following smoking are shown to largely reflect the reversal of deprivation effects. The drug × time interaction was non-significant (Table 3), as it was in both earlier studies (O'Neill and Parrott 1992; Parrott 1993). This consistency of drug effect over the day indicated that mood-modulation did not show acute tolerance. However, inspection of the mean values, shows that the amount of stress modulation did reduce over the day, with values of − 1.1, − 0.8, − 0.7, and − 0.5, for the four time blocks, respectively (Table 1). There are two possible explanations for this non-significant trend. Firstly, later cigarettes were acting against a background of accumulating plasma nicotine, and were therefore probably leading to less of an increase in nicotine concentration (Surgeon General 1988, p. 29–42; Russell 1989; Benowitz 1990). Secondly, with a diurnal pattern of decreasing stress, later cigarettes were acting upon lower baseline values, and thus the degree of possible stress-change was reduced. These two explanations may be related, since increasing plasma nicotine may be associated with reducing feelings of stress (as predicted by Warburton et al. 1988). It should be noted however, that a diurnal pattern of decreasing stress was also found with non-smokers, although the rate of stress-decrease was slightly greater with smokers (Parrott and Joyce 1993).

Self-rated feelings of arousal also fluctuated over the day, with low arousal pre-smoking, higher arousal post-smoking, and arousal decreasing in-between cigarettes (Parrott 1994). Self-rated arousal followed an inverted-U function over time, with low arousal in the morning, peak arousal mid-day, and reducing arousal in the evening. This pattern is typical of studies in the area (Folkard 1983). The drug × time interaction was significant, as it had been in O'Neill and Parrott (1992). In both studies, the increase in self-rated arousal was greatest for the first cigarette of the day. However, later cigarettes did not show a simple reduction in effect over time, as might be expected were acute tolerance in operation. Instead, the larger arousal increase after the first cigarette, may be caused by two factors other than tolerance. Firstly, it may

reflect overnight deprivation, with its correspondingly low level of plasma nicotine on waking. Thus the first cigarette of the day produces a larger increase in plasma nicotine than later cigarettes (Russell 1989; Benowitz 1990). Secondly, it may be influenced by the low level of arousal early in the day. The present data illustrate this factor. When pre-cigarette levels of arousal were high (cigarette blocks 2 and 3), then the arousal increase post-smoking was comparatively small (+ 0.3, + 0.4), whereas when pre-cigarette arousal levels were low (cigarette blocks 1 and 4), then the arousal increase post-smoking was slightly larger (+ 0.8, + 0.5, respectively; Table 2). [Note: the lesser change for cigarette blocks 2 and 3 does not reflect a "ceiling" effect, since the highest obtained mean score (6.8), was far short of the maximum possible (10.0)]. Perkins et al. (1992a, p. 131) also found that the effects of smoking/nicotine were dependent upon the pre-cigarette baseline: "Those initially low in arousal showed large increases following nicotine or smoking, whereas those high in arousal showed little change". Overall, therefore, it may be that the first cigarette of the day had the strongest influence upon feelings of arousal, for two reasons: overnight deprivation (with the first cigarette of the day producing the largest increase in plasma nicotine), and low early-morning arousal (with its greater potential for increased arousal). Alternatively, it may reflect true acute pharmacodynamic tolerance; only when the influence of the two other factors has been fully calculated, can the amount of true tolerance be estimated.

The five SMQ sedative subgroups reported different amounts of stress modulation. However, the degree of subjective change reported by each group was broadly consistent over the day (group × drug × time interaction: non-significant). Thus, high sedative smokers reported large amounts of stress modulation over all four time blocks, with high stress pre-smoking, and smoking leading to the normalisation of these deleterious mood states (Table 1). In contrast, low sedative smokers reported minimal stress modulation, again over the whole day (Table 1). A similar pattern was evident in the arousal data, with consistent amounts of arousal change being reported by each subgroup. Thus high stimulant smokers reported low pre-cigarette arousal, while smoking led to the normalisation of these low arousal states. This arousal, modulation was found with all cigarette blocks over the day. In contrast, low stimulant smokers reported minimal arousal change, again across all cigarette blocks (Table 2). The lack of arousal change with these latter smokers reflected their high arousal pre-smoking. Indeed, they reported high arousal even before their first cigarette of the day, and minimal change in arousal after that first cigarette (Table 2).

Overall therefore, there was little evidence of acute pharmacodynamic tolerance to the subjective effects of smoking, either with respect to stress or arousal. This conclusion differs from that offered by Rosenberg et al. (1980), and Russell (1989). They suggested that cognitive/mood effects only occur with cigarettes smoked against a background of clear nicotine deprivation. The present findings demonstrated that many smokers experience mood-modulation over the whole smoking day, and not just after their first cigarette. The main source of disagreement lies in the time-course for "deprivation" to occur. Russell (1989) concluded that overnight deprivation was required, for pharmacodynamic effects to be clearly evident. The present data suggested a far shorter period, possibly around 30 min (see Figs 4,5 in Parrott, 1994). Perkins et al. (1992b) suggested an even shorter timeframe, around 10 min. Whatever the actual time required (it may vary considerably between individuals and situations), the general pharmacodynamic pattern is of vacillating mood/cognitive states, with deleterious moods developing in-between cigarettes, and mood normalisation after smoking. West and Jarvis (1986) reported a similar pattern, in their study of two non-smokers administered 2 mg nicotine nasal spray, once every hour for 6 h. Vacillating task performance was evident, with faster tapping immediately after nicotine, but performance returning to baseline by the end of each hour (Fig. 2 in West and Jarvis 1986). They concluded that acute tolerance had not occurred. Their psychomotor task findings also agree closely with the present subjective arousal data (Table 2).

This study was concerned with the question of acute tolerance, but for tolerance to be demonstrated unambiguously, each dose of the drug needs to be given under the same basic conditions. It is this equality of background conditions, that is difficult to establish in smoking research. Future studies should therefore monitor nicotine plasma levels, pre-cigarette and post-cigarette, at each test point. This will enable the degree of pharmacodynamic change to be compared with any change in nicotine concentration. It may also be desirable to administer nicotine at regular time points, so that the inter-drug withdrawal period is constant (as in: West and Jarvis 1986). The final confounding factor is peculiar to pharmacodynamic research, namely the natural variation in mood/cognition/performance over the day (Folkard 1983; Parrott and Joyce 1993). This diurnal variation will often be difficult to control, but must be taken into account, when considering whether acute pharmacodynamic tolerance has occurred.

Acknowledgements. I would like to thank Dr. Alun Morinan, and Dr. Donald Smith for their valuable comments upon an earlier version of this paper.

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