Smoking, cortisol and nicotine

Andrew Steptoe [a,*], Michael Ussher [b]

[a] Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK
[b] Department of Community Health Sciences (Psychology), St. George's, University of London, Cranmer Terrace, London SW17 ORE, UK

Abstract

Cigarette smoking is associated acutely with elevated cortisol levels. However, the results of comparisons of cortisol levels in smokers and non-smokers have been inconsistent, and the significance of cortisol responses in smoking cessation is unclear. Here we describe one study comparing the cortisol profiles of smokers and nonsmokers over the day, and a second investigation in which cortisol was monitored during smoking cessation. In the first study, we collected saliva samples from 196 middle-aged men and women on working and weekend days repeatedly through the day. On both working and weekend days, cortisol levels were significantly higher in smokers after adjustment for age, gender and grade of employment. Cortisol responses to waking (the increase between waking and 30 min) were also greater in smokers.

The elevation in cortisol among smokers is generally attributed to nicotine exposure. Nicotine replacement therapy substantially improves abstinence rates, and has become a standard component of smoking cessation treatments, but the effects of nicotine replacement on cortisol are not known. In the second study, cortisol was monitored over 6 weeks of abstinence in 112 smokers treated with behavioural support and 15 mg nicotine patches. Smoking cessation was accompanied by an abrupt decrease in salivary cortisol, and this was sustained over the abstinence period. There was a marginal association between the decrease in cortisol and smoking relapse rates. These results suggest that the nicotine supplied through patches was not sufficient to block the cortisol reduction following smoking cessation. The contribution of these findings to understanding the role of neuroendocrine function in smoking is described.
© 2005 Elsevier B.V. All rights reserved.

Keywords: Smoking; Cortisol; Smoking cessation; Cortisol awakening response; Relapse

1. Introduction

Tobacco smoking has a wide range of biological effects that contribute to its negative impact on health. Apart from carcinogenic processes, these include the stimulation of vasomotor dysfunction, impaired endothelial-dependent vasodilatation, and the modification of lipid profiles (Ambrose and Barua, 2004; Celermajer et al., 1993). Smoking has marked inflammatory effects, causes acute increases in leukocyte counts, and is associated with elevated levels of inflammatory markers such as C-reactive protein, interleukin (IL) 6, and tumour necrosis factor α. It also stimulates platelet hyperaggregability, increased blood viscosity and reduced fibrinolysis (Barua et al., 2002).

Tobacco smoking and nicotine have pronounced effects on endocrine function as well. Nicotinic acetylcholine receptors are found throughout the central nervous system and also in peripheral tissues. There are several binding sites for nicotine within the paraventricular nucleus of the hypothalamus (Kellar et al., 1999), and the endocrine effects of nicotine appear to be the result of a combination of action at postsynaptic cholinergic sites that acutely regulate corticotrophin releasing factor (CRF), and presynaptic action on monoaminergic neurones (Pickworth and Fant, 1998). Acutely, smoking increases adrenocorticotrophic hormone (ACTH) and cortisol levels. This response appears to require quite intense intake, involving more than one cigarette (Gilbert et al., 1992; Kirschbaum et al., 1992), and has been attributed to nicotine exposure (Newhouse et al., 1990; Seyler et al., 1984). Interestingly, it has recently been established that nitric oxide is an inhibitory mediator of nicotine-induced hypothalamic–pituitary–adrenocortical (HPA) activity, providing a direct link between inflammatory

processes and the HPA activation stimulated by smoking (Gadek-Michalska and Bugajski, 2004).

The relationship between smoking, cortisol and nicotine is important for at least three reasons. First, the HPA axis is implicated in addictive processes, as discussed by other contributions to this special issue. Second, heightened levels of cortisol have a range of adverse effects on biological processes relevant to long-term health, including lipid profiles, immune function, central adiposity, bone mineral density and reproductive function (Steptoe and Ayers, 2004). Cortisol may therefore mediate some of the effects of smoking on health outcomes such as cardiovascular disease and the metabolic syndrome. Third, cortisol is highly sensitive to psychological stress. Smoking cessation is stressful for many smokers, and this may lead them to fail in quit attempts. It has been proposed that cortisol is directly involved in this process, and that changes in cortisol following smoking cessation may predict early relapse (al'Absi et al., 2004; Frederick et al., 1998).

Several aspects of the relationship between smoking and cortisol are discussed in other contributions. Here, we focus on two issues. The first is the relationship between habitual smoking and cortisol levels in everyday life; do smokers have higher, lower, or normal levels of cortisol? Second, we describe the pattern of cortisol change during a successful smoking cessation attempt supported by nicotine replacement, asking two questions: does cortisol concentration change with smoking cessation accompanied by nicotine replacement, and is it related to the likelihood of success in stopping smoking? Detailing these effects may help us to understand better the processes underlying smoking cessation.

2. Cortisol levels in habitual smokers

In view of the known acute effects of smoking on cortisol, it is perhaps surprising that the apparently simple question of whether cortisol levels differ in smokers and nonsmokers has not been satisfactorily answered. In an early study of 10 smoking and 15 nonsmoking premenopausal women, Yeh and Barbieri (1989) found no differences in 24-h urinary cortisol excretion levels. Kirschbaum et al. (1992) also studied 10 smokers with saliva samples every 20 min over 12 h of the day. They showed that cortisol output was elevated in smokers compared with nonsmokers. This is consistent with a large random sample of middle-aged men in the USA, in which serum cortisol concentrations were higher in smokers than nonsmokers (Field et al., 1994). By contrast, Handa et al. (1994) reported that middle-aged Japanese male smokers had lower plasma cortisol in the morning than did nonsmokers. Other studies that have assessed cortisol from plasma or saliva under resting conditions in the laboratory have shown mixed results, with higher levels in some studies (al'Absi et al., 2003; Baron et al., 1995), and no differences in others (Gossain et al., 1986; Kirschbaum et al., 1994; Tsuda et al., 1996).

Different methods of data collection and sample timing make it difficult to resolve these discrepancies. Since cortisol levels vary so markedly over the day, studies that do not take exact timing into account are difficult to interpret. Research in the literature has also varied in the extent to which other known correlates of cortisol such as age, gender and body mass have been taken into account. There is a consensus among most scientific workers in this field that salivary sampling provides the best method of studying cortisol profiles in free living individuals. Saliva sampling is unobtrusive in comparison with urine collection, and far less stressful than blood sampling, so that cortisol levels are unlikely to be affected by the data collection procedure (Kirschbaum and Hellhammer, 2000). Although levels of free cortisol in saliva are very low in comparison with serum values, the two sets of measures are strongly correlated. Moreover, cortisol in saliva is stable at room temperatures over several days, and this means that research participants can collect samples themselves and return them to the laboratory at their leisure. Data can therefore be efficiently collected from larger numbers of participants than is typically the case in studies involving blood or urine.

Cortisol levels are high in the early morning and diminish through the day, sometimes with a small secondary peak after a mid-day meal. There is growing evidence that the cortisol change over the first hour after waking represents a distinct psychobiological phenomenon that is under different control mechanisms from cortisol over the remainder of the day (Clow et al., 2004; Wust et al., 2000b). In the study described here, we therefore present separate results for cortisol over the day and the cortisol awakening response (CAR).

2.1. Methods

The data derive from a larger study of psychosocial factors related to biological activity in everyday life and physiological stress responses in the laboratory (Steptoe et al., 2002, 2003; Steptoe and Marmot, 2005). The relationship between the CAR and smoking was briefly described by Kunz-Ebrecht et al. (2004a), but none of these findings have been presented in detail before.

Data were collected from 103 men and 93 women aged 47–59 years who were part of the Whitehall II epidemiological study. The Whitehall study is a longitudinal observational investigation of psychosocial and biological determinants of coronary heart disease that was initiated in 1985–1988 with the recruitment of 10,308 British civil servants aged 35–55 years working in the London area (Marmot et al., 1991). A major interest in the Whitehall study is the socioeconomic gradient of disease risk, so participants in our substudy were systematically recruited from higher, intermediate and lower occupational grades. Occupational grade is strongly associated with other markers of socioeconomic position such as income and educational attainment. The study group participated in a laboratory mental stress testing session that is not discussed here, together with ambulatory blood pressure and heart rate monitoring over a working day. In addition, they collected saliva samples on a work day and a nonwork (weekend) day according to the following schedule: immediately after waking, 30 min later, and then at 8 2-h intervals from 08:00–08:30 to 22:00–22:30. Salivary free cortisol was assayed in Düsseldorf using a time-resolved immunoassay with fluorescence detection.
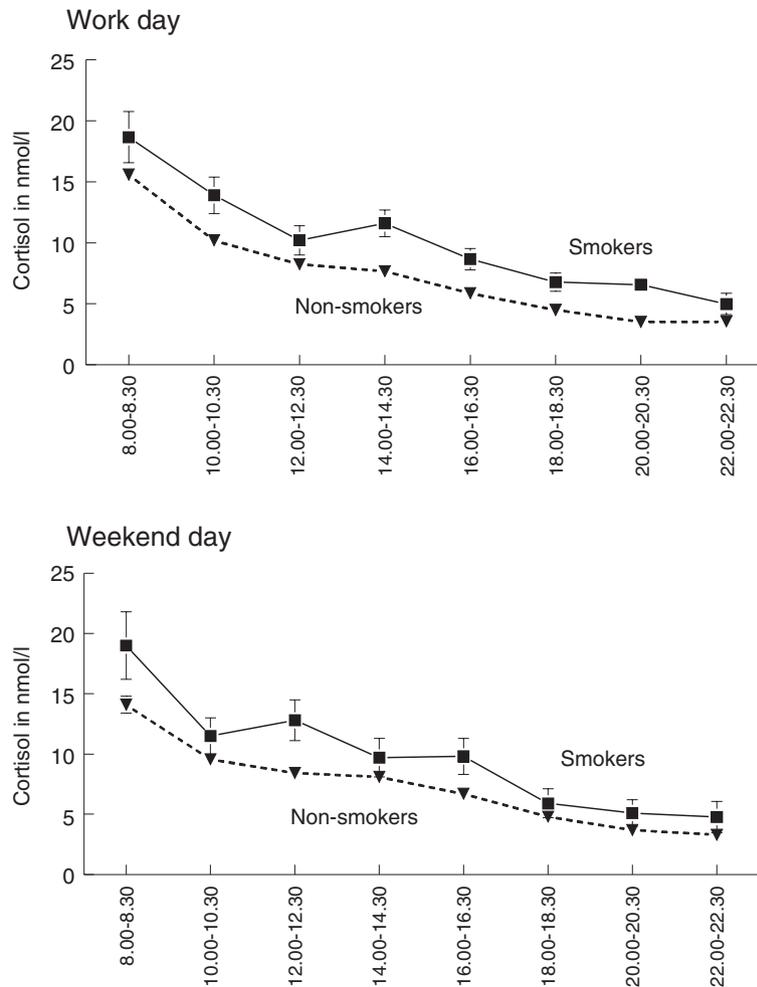
Fig. 1. Mean cortisol at eight times of the day and evening in smokers (solid line) and nonsmokers (dashed line), sampled over a working day (upper panel) and weekend day (lower panel). Data are adjusted for age, gender, and grade of employment (socioeconomic position). Error bars are standard errors of the mean (s.e.m.).

2.2. Cortisol profiles over the day and evening

Complete data for the eight timed samples were available from 167 participants over the working day: 15 smokers and 152 nonsmokers. These individuals did not differ from the remainder on any sociodemographic characteristics. Smokers and nonsmokers did not differ significantly in age or gender distribution. Smokers were more likely to work in lower grades of employment than nonsmokers ($\chi^2 = 4.04$, $P = 0.045$); this was expected, since there is a marked socioeconomic gradient in smoking in the UK, USA and many other countries. But smokers and nonsmokers did not differ in body mass index (BMI). Smokers and nonsmokers did not differ in time of waking up in the morning. The smokers reported an average intake of 12.2 (SD 7.3) cigarettes per day.

Fig. 1 summarises the mean levels of cortisol in smokers and nonsmokers over the working day (upper panel). Repeated measures analysis of variance with smoking status as the between-subject factor and time as the within-subject factor revealed main effects for smoking status ($F_{1165} = 12.80$, $P < 0.001$) and time of day ($F_{71155} = 57.39$, $P < 0.001$), with no interaction between the two. It can be seen that cortisol showed the expected decline over the day, but that levels were

slightly higher throughout in smokers than nonsmokers. This repeated measures analysis did not include covariates. We subsequently averaged the cortisol values, and compared smokers and nonsmokers in an analysis of covariance with age, gender, grade of employment, BMI and use of hormone replacement therapy (in women) as covariates. The effect of smoking status was once again significant ($F_{1159} = 11.76$, $P < 0.001$), with an average cortisol of 10.1 (SD 3.8) nmol/l in smokers (adjusted for covariates) and 7.23 (SD 2.8) nmol/l in nonsmokers. Thus, cortisol was just under 40% higher in smokers than nonsmokers.

Results for the weekend day are also shown in Fig. 1 (lower panel). One hundred sixty-eight participants had complete cortisol data available, and once again the main effect of smoking status was significant ($F_{1166} = 5.33$, $P = 0.022$). There was no interaction between smoking and time of day. Cortisol levels adjusted for age, gender, grade of employment, BMI and hormone replacement therapy averaged 9.90 (SD 4.4) and 7.34 (SD 3.3) nmol/l in smokers and nonsmokers respectively, a 35% difference.

These results indicate that cortisol is elevated over the day in smokers. Differences were present both on work days, when people's smoking was inevitably restricted by their work
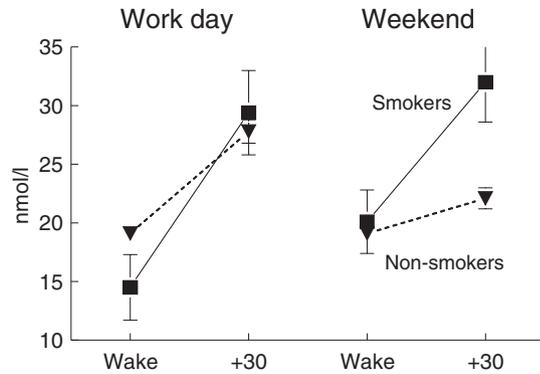
Fig. 2. Mean cortisol on waking (Wake) and 30 min later (+30) on a work day and weekend day in smokers (solid line) and non-smokers (dashed line). Results were adjusted for age, gender, grade of employment, and time of waking in the morning. Participants who did not obtain samples on the correct timing schedule were excluded. Error bars are s.e.m.

environments, and on leisure days. It is important to note that differences could not be attributed to other factors that might affect cortisol such as socioeconomic status and gender.

2.3. Cortisol awakening responses and cortisol

The CAR is the increase in cortisol that typically takes place over the first hour after waking, peaking at 20–45 min after waking up (Clow et al., 2004). The CAR appears to be partly under genetic control (Wust et al., 2000a), but also relates to health status and psychosocial experience. It appears to be unrelated to duration of sleep in healthy individuals. Larger CARs have been reported with a range of adverse psychosocial factors such as high work demands (Kunz-Ebrecht et al., 2004b; Schulz et al., 1998; Steptoe et al., 2004), perceived stress, clinical depression and depressive symptoms (Bhagwagar et al., 2003; Pruessner et al., 2003). The CAR is also larger on working than nonworking days (Kunz-Ebrecht et al., 2004a; Schlotz et al., 2004). On the other hand, a diminished CAR has been reported for people with physical health problems (Kudielka and Kirschbaum, 2003), people with chronic fatigue syndrome (Roberts et al., 2004), post-traumatic stress symptoms (Neylan et al., 2005) and a history of parental separation and/or death of a close relative in childhood (Meinlschmidt and Heim, 2005). Other factors such as burnout have produced mixed results (De Vente et al., 2003; Pruessner et al., 1999). The explanation for this variation is not yet clear. There may be a dimension of experience underlying these diverse phenomena that accounts for whether the CAR is heightened or reduced in a particular risk group. Results from smokers have also been inconsistent, with a reduced CAR being observed in one study (Wust et al., 2000b) and no differences in another (Edwards et al., 2001).

Two factors are important in making CAR comparisons between groups. The first is the time of waking, since there is evidence that the magnitude of the CAR is greater in people who wake earlier (Edwards et al., 2001; Kudielka and Kirschbaum, 2003). If the timing of waking is not assessed and taken into account statistically where necessary, a

misleading pattern of results might emerge. The second is the accuracy of timing of the waking sample. Since the CAR is a dynamic response, any delay in obtaining the first sample will result in the 'waking' value being taken on the upwards curve. The waking value will then be elevated, and the CAR will be reduced. We have demonstrated that a delay of more than 10 min between waking and taking the first sample can invalidate CAR assessment altogether (Wright and Steptoe, 2005).

In the present study, we assessed the CAR as the difference in cortisol between waking and 30 min later. Participants who delayed their waking sample more than 10 min were excluded. It is important to note that smoking was not permitted during this 30 min period, so any differences between smokers and nonsmokers do not reflect the acute effect of tobacco smoking.

One hundred and seventy-nine participants (14 smokers and 165 nonsmokers, 95 men, 84 women) provided CAR data on the working day and 171 on the nonworking day. The results are shown in Fig. 2. Repeated measures analysis of the working day revealed a 3-way interaction between smoking status, time, and gender ($F_{1175}=3.34$, $P=0.049$). We subsequently analysed the increase in cortisol between waking and 30 min, and this showed a larger CAR in smoking than nonsmoking men ($F_{189}=5.33$, $P=0.022$), after adjustment for age, grade of employment and time of waking in the morning. However, there was no difference in women.

The analysis of the CAR on the weekend day showed a simpler pattern of results. In the repeated measures analysis, the smoking status by time interaction was significant ($F_{1167}=6.57$, $P=0.011$), indicating that smokers and nonsmokers showed a different response pattern over time. When we analysed the increase between waking and 30 min, the difference remained significant after adjustment for gender, age, grade of employment and time of waking ($F_{1147}=7.23$, $P=0.008$). The mean adjusted increase was 12.3 (SD 13.6) nmol/l in smokers, and 2.57 (SD 11.0) nmol/l in nonsmokers.

The results of these analyses of the CAR thus present a rather less consistent picture than those for cortisol over the day. The CAR was elevated in both male and female smokers on the weekend day, but only among men on the work day. Additionally, the effect for male smokers on the work day is due in part to lower waking levels, rather than higher absolute cortisol at 30 min. This contrasts with the home day, in which smokers showed a substantially higher cortisol level 30 min after waking than did nonsmokers. We and others have previously showed that the CAR is reduced on nonworking compared with working days, and this is consistent with the CAR being an anticipatory response to the stress of the day (Kunz-Ebrecht et al., 2004a). What these data imply is that the diminution in the CAR on leisure days is much smaller for smokers than for nonsmokers.

2.4. Conclusions

The results of these analyses indicate that cortisol levels are elevated in everyday life among smokers compared with nonsmokers. The difference in values was quite substantial, averaging 35% or more on both working and weekend days. It
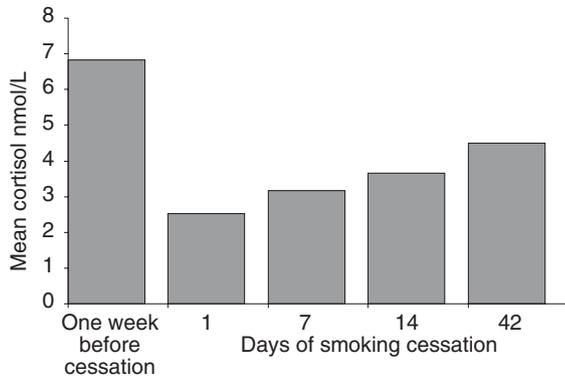
Fig. 3. Mean cortisol concentration for those providing data across all five measurement points following smoking cessation ($n = 30$).

is possible that previous studies have failed to observe consistent differences between smokers and nonsmokers because they used a single measure of cortisol, since similar findings to ours were reported by Kirschbaum et al. (1992) using serial saliva measures. There was also an association between the CAR and smoking, but this was less consistent than the results for the day and evening. We could not identify any other potential confounders that accounted for this pattern of results. Unfortunately, we did not have sufficient numbers in our sample to be able to analyse associations with the intensity of smoking.

3. Cortisol and smoking cessation

The second major issue addressed in this article is the pattern of cortisol change with smoking cessation. If cortisol levels are typically elevated in everyday life in smokers, does this mean that smoking cessation leads to a rebound decrease on stopping smoking? A number of studies have examined whether such a response occurs. Most have targeted smokers who are not using pharmaceutical aids to cessation and they have shown a significant decline in cortisol following periods of smoking abstinence ranging from 4 h to 6 weeks (Cohen et al., 2004; Gilbert et al., 1999; Pomerleau et al., 2000; Puddey et al., 1984). Several smaller and less rigorous studies have reported either no change, or an increase, in cortisol following smoking abstinence, and this has been observed both for people not using pharmaceutical aids to cessation (Benowitz et al., 1984; Hughes et al., 1988; Pickworth et al., 1996), and among those using nicotine patches (Pickworth et al., 1996; Teneggi et al., 2002). In addition, a greater decline in cortisol on quitting smoking has been found to be predictive of relapse to smoking and exacerbation of withdrawal symptoms (al'Absi et al., 2004; Frederick et al., 1998).

The change in cortisol from the first few days of abstinence through to several weeks of abstinence has not been assessed within a single study before. In the present investigation, we also sought to confirm the previous report of a reduction in cortisol predicting smoking relapse at one week through examining whether cortisol predicts relapse at 6 weeks (al'Absi et al., 2004). The present study was carried out as a secondary

analysis of data from a larger study of smokers trying to quit using nicotine patches (Ussher et al., 2003). The aim of the larger study was not primarily to evaluate the impact of nicotine patches per se, but rather to examine the effect of exercise on smoking abstinence. Therefore, a control group using placebo patches was not included and the primary aim of the present study was not to evaluate the impact of nicotine patches; rather we had an opportunity as part of the larger trial to examine cortisol during ad lib smoking and during the first day of abstinence through to 6 weeks of abstinence, and to relate cortisol to smoking relapse at 6 weeks. The relationship between cortisol, urges to smoke, cigarette withdrawal symptoms and stress, for this data, is investigated elsewhere (Ussher et al., in press).

3.1. Methods

One hundred and twelve males and females were assessed while smoking and for up to 6 weeks of an attempt at smoking abstinence. Participants were required to use one 15 mg 16-h nicotine patch each day, from the quit day through to 6 weeks of abstinence. A session of behavioural support towards stopping smoking was provided on an individual basis (Jorenby et al., 1995) for 5 weeks, commencing 1 week before the quit day and ending 4 weeks after cessation. In addition, a follow-up session took place 2 weeks after the final treatment.

Baseline data included expired air carbon monoxide (CO), the Fagerström Test for Nicotine Dependence (FTND, Heatherton et al., 1991), and self-reported physical activity levels (Blair et al., 1985). Physical activity was assessed again 1 week and 6 weeks after the quit day. At each treatment session, self-reported abstinence from smoking was verified with expired CO (<10 ppm). Those withdrawing from the study were considered as having lapsed (Hughes et al., 2003).

An ad lib smoking measure of salivary cortisol was taken 1 week before smoking cessation. To avoid the acute effects of smoking, participants abstained from smoking for at least 30 min prior to this measure. Abstinent smokers provided further saliva samples after abstinence of 1 day, 1 week, 2 weeks and 6 weeks. On each occasion a single saliva sample was taken at 16.00–17.00 h. Cortisol levels in a sample taken in the late afternoon correlate highly with a measure of diurnal cortisol (Edwards et al., 2001). An enzyme linked immunoassay (Salimetrics LLC) was used to determine cortisol concentration.

3.2. Smoking abstinence

Of the initial 112 smokers (77 female, mean (SD) age=42.6 (11.4), mean (SD) cigarettes per day=20.7 (7.9), data were only gathered for those maintaining continued abstinence from smoking. The rates of abstinence at each time following the quit day were: 1 day 89.3% (100/112), 1 week 83.0% (93/112), 2 weeks 67.0% (75/112) and 6 weeks 53.6% (60/112). Thirty participants were both abstinent for 6 weeks and provided cortisol samples at all five measurement times. There was a significantly higher number of women ($P = 0.012$) in the latter

sub-sample ($N=30$) versus the remaining participants. There were no other significant differences between those who provided all cortisol samples and the remainder.

3.3. Changes in cortisol

The data for cortisol concentration were strongly positively skewed; therefore for all analyses of the cortisol data non-parametric tests were used. For those providing cortisol at all 5 measurement times (see Fig. 3), there was a significant reduction in cortisol for 1 week pre-abstinence cortisol versus abstinence of 1 day (Wilcoxon $Z=3.1$, $P=0.002$), 1 week ($Z=2.8$, $P=0.005$), 2 weeks ($Z=2.2$, $P=0.026$) and 6 weeks ($Z=2.3$, $P=0.023$). As a secondary analysis, we included all those providing a cortisol sample at any time point. Once again, Wilcoxon tests showed a significant reduction in cortisol between pre-abstinence and abstinence of 1 day ($N=82$, mean (SD) cortisol: pre-abstinence $=5.1$ (8.0), 1 day $=3.1$ (4.7), $Z=2.7$, $P=0.006$), 1 week ($N=66$, mean (SD) cortisol: pre-abstinence $=5.9$ (9.1), 1 week $=4.20$ (8.3), $Z=2.5$, $P=0.012$) and 6 weeks ($N=49$, mean (SD) cortisol: pre-abstinence $=7.7$ (11.3), 6 weeks $=5.9$ (9.8), $Z=2.1$, $P=0.038$). For the secondary analysis, there was not a significant difference in cortisol between pre-cessation and 2 weeks of cessation ($Z=1.6$, $P=0.103$). In both the primary and secondary analyses, cortisol tended (non-significantly) to increase between 1 day and 6 weeks of abstinence (see Fig. 3).

3.4. Tobacco dependence/consumption and smoking relapse

A greater reduction in cortisol between pre-abstinence and 1 day of abstinence was significantly related to reports of smoking a greater number of cigarettes (Spearman's $\rho=0.3$, $P=0.008$, $N=82$) and was related, with marginal significance, to FTND score and expired CO ($P=0.051$ and 0.089, respectively). Neither cortisol at pre-abstinence nor cortisol following 1 day of abstinence were significantly related to pre-abstinence expired CO or to FTND score. However, a greater number of cigarettes smoked per day was positively related to cortisol at pre-abstinence ($\rho=0.2$, $P=0.013$, $N=112$), but was not significantly related to cortisol on the first day of cessation.

A greater decline in cortisol between pre-abstinence and 1 day of abstinence was marginally predictive of higher rates of relapse at 6 weeks (Mann Whitney $Z=1.8$, $P=0.073$, $N=82$). There was no indication of a significant relationship between absolute levels of cortisol at pre-abstinence or on the first day of abstinence and rates of relapse at 6 weeks.

3.5. Possible confounders

There was no significant difference between the primary pre-abstinence cortisol measure, obtained 1 week before smoking cessation, and a secondary pre-abstinence measure taken on the quit day (Wilcoxon test). This suggests that the primary pre-abstinence measure of cortisol provides a reliable measure of cortisol during ad lib smoking. Additionally,

cortisol values at all time points were significantly correlated with each other (all at $P<0.01$, Spearman's ρ range: $=0.3–0.8$). This provides support for the intra-individual stability of the cortisol measures.

We also considered the extent of use of nicotine patches as a confounder. Following smoking abstinence of 1 week and 2 weeks, nearly all the participants reported using patches each day (92% and 93.0%, respectively). However, after abstinence of 6 weeks only 63% (31/49) of the participants reported using patches. Use of patches at 6 weeks was not significantly related to the change in cortisol between pre-abstinence and 1 week or 6 weeks, or to cortisol at pre-abstinence (Mann Whitney test).

When considering other confounders, neither the absolute level of cortisol at pre-abstinence or on the first day of abstinence, nor the change in cortisol between pre-abstinence and the first day of cessation, were significantly related to gender, self-reported physical activity levels, assignment to exercise or control condition in the larger trial, time since last cigarette or last meal at pre-abstinence, body mass index, grade of employment or age (Spearman's rank correlations and Mann Whitney tests). Thus, we would argue that the associations between cortisol change and smoking cessation are genuine responses to stopping smoking.

3.6. Conclusions

Our findings indicate that smokers using 15 mg nicotine patches are likely to experience a sharp decline in cortisol on the first day of smoking cessation which is maintained through to 6 weeks of cessation. Cortisol did not increase significantly between abstinence of 1 day and 6 weeks and heavier smokers were more likely to experience a decline in cortisol. Together, the latter findings suggest that the reduction in cortisol is probably an 'offset' effect, related to a fall in levels of nicotine or other constituents of tobacco smoke. This is consistent with the findings from the first study showing moderately elevated cortisol in everyday life among smokers. There was a tendency (though only marginally significant) for a greater reduction in cortisol following smoking abstinence to be associated with increased relapse to smoking at 6 weeks. This resembles the previous report from al'Absi et al. (2004) that showed similar effects over the first week of abstinence. This result might seem paradoxical; if smoking elevated cortisol, why should a greater 'normalisation' following cessation predict later relapse? It is possible that the cortisol secretion patterns of future smokers differ from those of nonsmokers, and that this is relevant to the magnitude of reductions after cessation. Unfortunately, there is little evidence relating cortisol secretion patterns with smoking risk, but there are suggestive findings for other addictive behaviours (King et al., 2002). Another possibility is that the size of the cortisol reduction is a marker of dependence. This is supported by our observation of a significant association between the cortisol change over the first day of abstinence and smoking intensity. Highly nicotine dependent smokers are more likely to fail in quit attempts, and this may be reflected in the correlation between cortisol decrease and relapse. However, controlled studies with larger samples are required to establish

whether a reduction cortisol is a reliable predictor of smoking relapse. In order to determine whether nicotine patches have the potential to counteract the reduction in cortisol following smoking cessation, studies are also required comparing the decline in cortisol after stopping smoking for various strengths of nicotine patches versus placebo patches.

Acknowledgements

References

al'Absi, M., Wittmers, L.E., Erickson, J., Hatsukami, D., Crouse, B., 2003. Attenuated adrenocortical and blood pressure responses to psychological stress in ad libitum and abstinent smokers. Pharmacol. Biochem. Behav. 74, 401–410.

al'Absi, M., Hatsukami, D., Davis, G.L., Wittmers, L.E., 2004. Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. Drug Alcohol Depend. 73, 267–278.

Ambrose, J.A., Barua, R.S., 2004. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J. Am. Coll. Cardiol. 43, 1731–1737.

Baron, J.A., Comi, R.J., Cryns, V., Brinck-Johnsen, T., Mercer, N.G., 1995. The effect of cigarette smoking on adrenal cortical hormones. J. Pharmacol. Exp. Ther. 272, 151–155.

Barua, R.S., Ambrose, J.A., Saha, D.C., Eales-Reynolds, L.J., 2002. Smoking is associated with altered endothelial-derived fibrinolytic and antithrombotic factors: an in vitro demonstration. Circulation 106, 905–908.

Benowitz, N.L., Kuyt, F., Jacob III, P., 1984. Influence of nicotine on cardiovascular and hormonal effects of cigarette smoking. Clin. Pharmacol. Ther. 36, 74–81.

Bhagwagar, Z., Hafizi, S., Cowen, P.J., 2003. Increase in concentration of waking salivary cortisol in recovered patients with depression. Am. J. Psychiatry 160, 1890–1891.

Blair, S.N., Haskell, W.L., Ho, P., Paffenbarger Jr., R.S., Vranizan, K.M., Farquhar, J.W., Wood, P.D., 1985. Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. Am. J. Epidemiol. 122, 794–804.

Celermajer, D.S., Sorensen, K.E., Georgakopoulos, D., Bull, C., Thomas, O., Robinson, J., Deanfield, J.E., 1993. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation 88, 2149–2155.

Clow, A., Thorn, L., Evans, P., Hucklebridge, F., 2004. The awakening cortisol response: methodological issues and significance. Stress 7, 29–37.

Cohen, L.M., al'Absi, M., Collins Jr., F.L., 2004. Salivary cortisol concentrations are associated with acute nicotine withdrawal. Addict. Behav. 29, 1673–1678.

De Vente, W., Olff, M., Van Amsterdam, J.G., Kamphuis, J.H., Emmelkamp, P.M., 2003. Physiological differences between burnout patients and healthy controls: blood pressure, heart rate, and cortisol responses. Occup. Environ. Med. 60 (Suppl 1), i54–i61.

Edwards, S., Evans, P., Hucklebridge, F., Clow, A., 2001. Association between time of awakening and diurnal cortisol secretory activity. Psychoneuroendocrinology 26, 613–622.

Field, A.E., Colditz, G.A., Willett, W.C., Longcope, C., McKinlay, J.B., 1994. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. J. Clin. Endocrinol. Metab. 79, 1310–1316.

Frederick, S.L., Reus, V.I., Ginsberg, D., Hall, S.M., Munoz, R.F., Ellman, G., 1998. Cortisol and response to dexamethasone as predictors of withdrawal distress and abstinence success in smokers. Biol. Psychiatry 43, 525–530.

Gadek-Michalska, A., Bugajski, J., 2004. Role of nitric oxide in the nicotine-induced pituitary-adrenocortical response. J. Physiol. Pharmacol. 55, 443–455.

Gilbert, D.G., Meliska, C.J., Williams, C.L., Jensen, R.A., 1992. Subjective correlates of cigarette-smoking-induced elevations of peripheral beta-endorphin and cortisol. Psychopharmacology (Berl) 106, 275–281.

Gilbert, D.G., McClernon, F.J., Rabinovich, N.E., Dibb, W.D., Plath, L.C., Hiyane, S., Jensen, R.A., Meliska, C.J., Estes, S.L., Gehlbach, B.A., 1999. EEG, physiology, and task-related mood fail to resolve across 31 days of smoking abstinence: relations to depressive traits, nicotine exposure, and dependence. Exp. Clin. Psychopharmacol. 7, 427–443.

Gossain, V.V., Sherma, N.K., Srivastava, L., Michelakis, A.M., Rovner, D.R., 1986. Hormonal effects of smoking—II: Effects on plasma cortisol, growth hormone, and prolactin. Am. J. Med. Sci. 291, 325–327.

Handa, K., Kono, S., Ishii, H., Shinchi, K., Imanishi, K., Arakawa, K., 1994. Relationship of alcohol consumption and smoking to plasma cortisol and blood pressure. J. Hum. Hypertens 8, 891–894.

Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerstrom, K.O., 1991. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br. J. Addict. 86, 1119–1127.

Hughes, J.R., Arana, G., Amori, G., Stewart, F., Workman, R., 1988. Effect of tobacco withdrawal on the dexamethasone suppression test. Biol. Psychiatry 23, 96–98.

Hughes, J.R., Keely, J.P., Niaura, R.S., Ossip-Klein, D.J., Richmond, R.L., Swan, G.E., 2003. Measures of abstinence in clinical trials: issues and recommendations. Nicotine Tob. Res. 5, 13–25.

Jorenby, D.E., Smith, S.S., Fiore, M.C., Hurt, R.D., Offord, K.P., Croghan, I.T., Hays, J.T., Lewis, S.F., Baker, T.B., 1995. Varying nicotine patch dose and type of smoking cessation counselling. J.A.M.A. 274, 1347–1352.

Kellar, K.J., Davila-Garcia, M.I., Xiao, Y., 1999. Pharmacology of neuronal nicotinic acetylcholine receptors: effects of acute and chronic nicotine. Nicotine Tob. Res. 1 (Suppl 2), S117–S120.

King, A.C., Schluger, J., Gunduz, M., Borg, L., Perret, G., Ho, A., Kreek, M.J., 2002. Hypothalamic–pituitary–adrenocortical (HPA) axis response and biotransformation of oral naltrexone: preliminary examination of relationship to family history of alcoholism. Neuropsychopharmacology 26, 778–788.

Kirschbaum, C., Hellhammer, D.H., 2000. Salivary cortisol. In: Fink, G. (Eds.) Encyclopedia of Stress, vol. 3. Academic Press, San Diego, pp. 379–383.

Kirschbaum, C., Wust, S., Strasburger, C.J., 1992. 'Normal' cigarette smoking increases free cortisol in habitual smokers. Life Sci. 50, 435–442.

Kirschbaum, C., Scherer, G., Strasburger, C.J., 1994. Pituitary and adrenal hormone responses to pharmacological, physical, and psychological stimulation in habitual smokers and nonsmokers. Clin. Investig. 72, 804–810.

Kudielka, B.M., Kirschbaum, C., 2003. Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. Psychoneuroendocrinology 28, 35–47.

Kunz-Ebrecht, S.R., Kirschbaum, C., Marmot, M., Steptoe, A., 2004. Differences in cortisol awakening response on work days and weekends in women and men from the Whitehall II cohort. Psychoneuroendocrinology 29, 516–528.

Kunz-Ebrecht, S.R., Kirschbaum, C., Steptoe, A., 2004. Work stress, socioeconomic status, and neuroendocrine activation over the working day. Soc. Sci. Med. 58, 1523–1530.

Marmot, M.G., Davey Smith, G., Stansfeld, S., Patel, C., North, F., Head, J., White, I., Brunner, E., Feeney, A., 1991. Health inequalities among British civil servants: the Whitehall II study. Lancet 337, 1387–1393.

Meinlschmidt, G., Heim, C., 2005. Decreased cortisol awakening response after early loss experience. Psychoneuroendocrinology 30, 568–576.

Newhouse, P.A., Sunderland, T., Narang, P.K., Mellow, A.M., Fertig, J.B., Lawlor, B.A., Murphy, D.L., 1990. Neuroendocrine, physiologic and behavioral responses following intravenous nicotine in nonsmoking healthy volunteers and in patients with Alzheimer's disease. Psychoneuroendocrinology 15, 471–484.

Neylan, T.C., Brunet, A., Pole, N., Best, S.R., Metzler, T.J., Yehuda, R., Marmar, C.R., 2005. PTSD symptoms predict waking salivary cortisol levels in police officers. Psychoneuroendocrinology 30, 373–381.

Pickworth, W.B., Fant, R.V., 1998. Endocrine effects of nicotine administration, tobacco and other drug withdrawal in humans. Psychoneuroendocrinology 23, 131–141.

Pickworth, W.B., Baumann, M.H., Fant, R.V., Rothman, R.B., Henningfield, J.E., 1996. Endocrine responses during acute nicotine withdrawal. Pharmacol. Biochem. Behav. 55, 433–437.

Pomerleau, O.F., Pomerleau, C.S., Marks, J.L., 2000. Abstinence effects and reactivity to nicotine during 11 days of smoking deprivation. Nicotine Tob. Res. 2, 149–157.

Pruessner, J.C., Hellhammer, D.H., Kirschbaum, C., 1999. Burnout, perceived stress, and cortisol responses to awakening. Psychosom. Med. 61, 197–204.

Pruessner, M., Hellhammer, D.H., Pruessner, J.C., Lupien, S.J., 2003. Self-reported depressive symptoms and stress levels in healthy young men: associations with the cortisol response to awakening. Psychosom. Med. 65, 92–99.

Puddey, I.B., Vandongen, R., Beilin, L.J., English, D., 1984. Haemodynamic and neuroendocrine consequences of stopping smoking—a controlled study. Clin. Exp. Pharmacol. Physiol. 11, 423–426.

Roberts, A.D., Wessely, S., Chalder, T., Papadopoulos, A., Cleare, A.J., 2004. Salivary cortisol response to awakening in chronic fatigue syndrome. Br. J. Psychiatry 184, 136–141.

Schlotz, W., Hellhammer, J., Schulz, P., Stone, A.A., 2004. Perceived work overload and chronic worrying predict weekend–weekday differences in the cortisol awakening response. Psychosom. Med. 66, 207–214.

Schulz, P., Kirschbaum, C., Pruessner, J., Hellhammer, D., 1998. Increased free cortisol secretion after awakening in chronically stressed individuals due to work overload. Stress Med. 14, 91–97.

Seyler Jr., L.E., Fertig, J., Pomerleau, O., Hunt, D., Parker, K., 1984. The effects of smoking on ACTH and cortisol secretion. Life Sci. 34, 57–65.

Steptoe, A., Ayers, S., 2004. Stress, health and illness. In: Sutton, S., Baum, A., Johnston, M. (Eds.), Sage Handbook of Health Psychology. Sage, London, pp. 169–196.

Steptoe, A., Marmot, M., 2005. Socioeconomic position and coronary heart disease: a psychobiological perspective. In: Waite, L.J. (Ed.), Aging, Health, and Public Policy. Population Council, New York.

Steptoe, A., Feldman, P.M., Kunz, S., Owen, N., Willemsen, G., Marmot, M., 2002. Stress responsivity and socioeconomic status: a mechanism for increased cardiovascular disease risk? Eur. Heart J. 23, 1757–1763.

Steptoe, A., Kunz-Ebrecht, S., Owen, N., Feldman, P.J., Willemsen, G., Kirschbaum, C., Marmot, M., 2003. Socioeconomic status and stress-related biological responses over the working day. Psychosom. Med. 65, 461–470.

Steptoe, A., Siegrist, J., Kirschbaum, C., Marmot, M., 2004. Effort-reward imbalance, overcommitment, and measures of cortisol and blood pressure over the working day. Psychosom. Med. 66, 323–329.

Teneggi, V., Tiffany, S.T., Squassante, L., Milleri, S., Ziviani, L., Bye, A., 2002. Smokers deprived of cigarettes for 72 h: effect of nicotine patches on craving and withdrawal. Psychopharmacology (Berl) 164, 177–187.

Tsuda, A., Steptoe, A., West, R., Fieldman, G., Kirschbaum, C., 1996. Cigarette smoking and psychophysiological stress responsiveness: effects of recent smoking and temporary abstinence. Psychopharmacology 126, 226–233.

Ussher, M., West, R., McEwen, A., Taylor, A., Steptoe, A., 2003. Efficacy of exercise counselling as an aid for smoking cessation: a randomized controlled trial. Addiction 98, 523–532.

Ussher, M., West, R., Evans, P., Steptoe, A., McEwen, A., Clow., A., Hucklebridge, F., in press. Reduction in cortisol following smoking cessation among users of nicotine patches. Psychosom. Med.

Wright, C.E., Steptoe, A., 2005. Subjective socioeconomic position, gender and cortisol responses to waking in an elderly population. Psychoneuroendocrinology 30, 582–590.

Wust, S., Federenko, I., Hellhammer, D.H., Kirschbaum, C., 2000. Genetic factors, perceived chronic stress, and the free cortisol response to awakening. Psychoneuroendocrinology 25, 707–720.

Wust, S., Wolf, J., Hellhammer, D.H., Federenko, I., Schommer, N., Kirschbaum, C., 2000. The cortisol awakening response — normal values and confounds. Noise Health 7, 77–85.

Yeh, J., Barbieri, R.L., 1989. Twenty-four-hour urinary-free cortisol in premenopausal cigarette smokers and nonsmokers. Fertil. Steril. 52, 1067–1069.