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International Journal of Psychophysiology 59 (2006) 236 – 243
INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY
www.elsevier.com/locate/ijpsycho

The hypothalamic–pituitary–adrenal (HPA) axis in habitual smokers

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Received 13 October 2005; received in revised form 15 October 2005; accepted 20 October 2005
Available online 2 December 2005

Abstract

Nicotine is a strong activator of the hypothalamus pituitary adrenal (HPA) axis. Smoking of only two cigarettes consistently activates the HPA axis of habitual smokers. However, while being a habitual smoker only induces small changes of basal HPA axis activity, smoking induces an attenuated responsiveness of the HPA axis to psychological stress, but not to injection of corticotropin releasing hormone (CRH) or physiological load. The latter points to alterations at hypothalamic or other central structures. The further consequences of decreased HPA axis responsiveness are discussed. Chronic inflammation of the airways is a common consequence of habitual smoking, and smokers often present with low-grade systemic inflammation, which may be mediated by HPA axis alterations. However, habitual smokers' monocytes are reported to show an increased sensitivity towards the inflammation suppressing effects of cortisol, while on the one hand, inflammation of the airways appears to be relatively resistant towards glucocorticoid treatment. In conclusion, this pattern of attenuated cortisol responses and decreased glucocorticoid sensitivity may be causally related to disinhibition of inflammatory processes and thereby further stimulate adverse health outcomes, such as airway inflammation or atherosclerosis.

Keywords: Nicotine; Cigarette smoking; Tobacco; Cortisol; HPA axis; Chronic low-grade inflammation; Airway inflammation; Psychosocial stress

1. Introduction

Cigarette smoking is a common habit in many developed and even more in developing countries. It is assumed that around 25% of the people living in developed countries are habitual cigarette smokers (Zaher et al., 2004). The Centers for Disease Control (CDC) define current smokers as people reporting to have smoked at least 100 cigarettes during their lifetimes and consuming cigarettes every day or some days (CDC, 2002). However, the typical number of cigarettes consumed by a habitual smoker is 15 per day (varying from 14/day in low-income countries to 22/day in high-income countries; Zaher et al., 2004). Most of the studies summarized in this review define subjects as habitual smokers if a minimum number of 10 to 15 cigarettes is smoked per day. The negative health consequences of chronic cigarette smoking are well known: Smokers have higher rates of inflammatory diseases of the airways, such as asthma or chronic obstructive airway disease (COPD), cardiovascular diseases, and lung cancer. Altogether making chronic tobacco use a major cause of morbidity and mortality, with about 3 million deaths world wide attributable to tobacco use (Zaher et al., 2004).

Cigarette smoke has more than 1000 components, the effects of which are only partially understood today. Nicotine as one of the best-known components has profound effects on the central nervous system. Mediated by nicotine binding to nicotinic acetylcholinergic receptors, each cigarette smoked induces significant changes in many brain systems. One of the systems affected is the hypothalamic–pituitary–adrenal (HPA) axis, which is activated by single doses of nicotine to secrete corticotropin-releasing hormone (CRH) in the paraventricular nucleus of the hypothalamus, followed by adrenocorticotropic hormone (ACTH) secretion from the pituitary and cortisol secretion by the adrenal glands. Chronic nicotine exposure alters basal HPA axis activity and the reactivity to psychosocial stress. As the HPA axis is involved in containment of inflammatory responses, we will discuss here the potential association of altered HPA axis activity and the disinhibition of the inflammatory system in smokers.

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doi:10.1016/j.ijpsycho.2005.10.012

2. Cigarette smoking stimulates the HPA axis

The first paper reporting changes of a hormone associated with the HPA axis, i.e., vasopressin, after cigarette smoking was published in 1949 by Walker (Walker, 1949). The first article, however, that explicitly reported smoking effects on the secretion of adrenocortical hormones was published in 1961 by Hökfelt (Hokfelt, 1961), followed by an Italian language article in 1967 (Santagati et al., 1967), and another English language publication in 1968 in the Journal of the American Medical Association (JAMA; Kershbaum et al., 1968). These and further early articles showed that smoking of high-nicotine cigarettes induced large increases in plasma glucocorticoid concentrations (see also Hill and Wynder, 1974; Cryer et al., 1976, and Winternitz and Quillen, 1977). Hill and Wynder, and Cryer et al. additionally reported that smoking induced the release of epinephrine and norepinephrine and stimulated heart rate and blood pressure (Hill and Wynder, 1974). Cryer et al. were able to prevent the latter by adrenergic blockade. They were also the first to report an increase in plasma growth hormone (GH) in response to cigarette smoking (Cryer et al., 1976). Winternitz and Quillen were the first to report a dose-dependency of nicotine-induced HPA axis stimulation (Winternitz and Quillen, 1977).

The same effect, i.e., a dose-dependent stimulation of the HPA axis was also reported in rats with i.p. injection of 100, 200, or 500 mg/kg nicotine. While the maximum corticosterone response was observed with the highest nicotine concentration, the authors further report that with higher dosage, nicotine elicits a biphasic response, with an immediate corticosterone peak during the first 15 min, and a second and higher peak 20 min after injection. The ACTH response only showed a single peak. Hypophysectomy completely abolished HPA responses to nicotine (Cam and Bassett, 1983; Cam et al., 1979).

In the following years, several aspects of the HPA axis response to nicotine, in human studies mostly delivered by cigarettes, in animal studies by injection, have been investigated in more detail.

2.1. Dose-dependency and threshold level of nicotine

The first to report a dose-dependency of nicotine induced HPA axis activation in humans were Winternitz and Quillen (see above, 1977). They reported that at least two high nicotine cigarettes have to be smoked to induce a sharp increase of plasma cortisol and GH. Using cigarettes with 1.5 and 0.08 mg nicotine and the experimental condition “sham smoking”, Spohr et al. showed associations of plasma levels of nicotine with simultaneous increases of blood pressure and heart rate, as well as delayed increases of plasma cortisol in six habitual smokers (Spohr et al., 1979). In another study male habitual smokers smoked two cigarettes containing either 2.0 or 0.2 mg nicotine. Again a dose-dependent increase of cortisol, GH, and prolactin was reported (Wilkins et al., 1982). Similar results were obtained by Seyler using cigarettes containing 2.87 or 0.48 mg nicotine (Seyler et al., 1986). Kirschbaum reported in 1992 that habitual smokers had to smoke two cigarettes of their preferred brand to elicit a significant increase in salivary free cortisol, while smoking only one cigarette was not sufficient (Kirschbaum et al., 1992).

Some studies also reported finding no increases of salivary cortisol after smoking (Cherek et al., 1982). Since in this study several cigarettes were smoked during a longer experimental session, it is unclear whether the time period between single cigarettes was short enough to reach a threshold level of nicotine for HPA activation. Pomerleau and Pomerleau only found a trend to increased cortisol in eight habitual smokers after smoking one cigarette (Pomerleau and Pomerleau, 1990a), while strong increases were found in another study where five habitual smokers smoked two high nicotine cigarettes (Pomerleau and Pomerleau, 1990b).

The issue of dose-dependency has also been investigated in animal studies. Cam et al. (1979, 1983, see above) reported a dose-dependent increase of ACTH and corticosterone by i.p. injection of nicotine in rather high concentrations of 200, 500, and 1000 mg/kg body weight. A later study using much lower concentrations was able to determine a threshold dose of 0.1 to 0.25 mg/kg body weight nicotine for HPA axis activation as measured by ACTH levels (Sharp and Beyer, 1986). A similar dose–response relationship was also found after i.v. injection of nicotine in doses between 65 and 2100 mg/kg body weight (Weidenfeld et al., 1989).

Intravenous nicotine injections to determine dose–response relationships have also been done in non-smokers. Newhouse et al. (1990) employed a continuous injection of 0.125, 0.25, and 0.5mg/kg/min nicotine in 11 healthy non-smokers for one hour (resulting in total nicotine doses of 7.5, 15, and 30 mg/kg). ACTH, cortisol, and prolactin in plasma, as well as self-reported mood and anxiety showed dose-dependent responses, i.e., anxiety increased and mood decreased with increasing nicotine doses (Newhouse et al., 1990). In contrast to this observation in non-smokers, Pomerleau and Pomerleau reported dose-related mood increases in smokers (Pomerleau and Pomerleau, 1992). In another study using 0.25 and 0.5mg/kg/min infusions for 30 min (i.e., 7.5 and 15 mg/kg nicotine), no significant increases of plasma cortisol were found. However, the nicotine concentration was sufficient to induce increases of epinephrine and norepinephrine already 15 min after beginning of the infusion and peak levels at the end of the infusion period (Andersson et al., 1993). An interesting way of nicotine application to human smokers and non-smokers was developed by Pomerleau et al. Intranasal application of 0.05, 1.00 and 2.00 mg nicotine resulted in similar nicotine concentrations as well as dose-dependent activation of physiological and endocrine responses (Pomerleau et al., 1992).

These latter infusion studies point to a threshold dose for HPA axis activation between 15 and 30 mg/kg body weight nicotine in healthy non-smokers using i.v. infusion. This is especially interesting, as much lower doses are required by habitual smokers when nicotine is inhaled with tobacco smoke. The way of application seems to modulate the extent of the endocrine response, with cigarette smoking inducing greater increases than other ways of application. This is also

corrobated by data from Benowitz et al. They compared three ways of nicotine application, i.e., cigarette smoking, nasal spray and transdermal application. It was found that although nicotine doses were kept comparable (16 cigarettes containing around 1 mg, 24×1 mg intranasal, and 15 mg in 16 h transdermal, resp.), endocrine responses were highest when subjects smoked (Benowitz et al., 2002).

Although some of the studies summarized above included male and female subjects, none explicitly reported sex differences in responsiveness of the HPA axis to cigarette smoking. In animals, however, pronounced sex differences in HPA axis responsiveness to nicotine are reported. Male and female Sprague–Dawley rats injected i.p. with 0, 0.03, 0.1, 0.3 or 0.5 mg/kg nicotine show a sex-specific activation pattern. In male rats, the AVP response was higher, while female rats secreted more ACTH and corticosterone (Rhodes et al., 2001). Furthermore, ACTH and corticosterone responses to medium nicotine doses vary with estrous cycle of female rats, showing highest increases in the proestrus and estrus phase (Rhodes et al., 2004).

Although some studies most likely included older subjects, age differences in HPA axis responses to acute cigarette smoking are rarely reported. In a study looking for age-differences in vasopressin responses, Chiodera et al. employed different paradigms to stimulated vasopressin release in 30 healthy men aged between 22 and 81 years, which were divided into three age groups. Cigarette smoking increased plasma vasopressin in all groups, but highest increases were found in the oldest group (Chiodera et al., 1991).

2.2. Mechanism of HPA axis activation by nicotine

It became clear in several early lesion and receptor-blockade studies that the HPA axis is stimulated at a central level, i.e., at the level of the hypothalamus,. At first, animal studies revealed that HPA axis activation by nicotine could be abolished by hypophysectomy, showing the involvement of ACTH from the anterior pitutiary (Cam et al., 1979). Weidenfeld et al. were then able to block HPA axis activation after i.v. nicotine by a nicotinic antagonist (mecamyline), by pretreatment with dexamethasone, and by hypothalamic lesions in the paraventricular nucleus (Weidenfeld et al., 1989). Marty et al., demonstrated in isolated perfused mouse brains that nicotine stimulates ACTH release, while in pituitary preparations, no such effect was observed (Marty et al., 1985). Another group congruently reported that the cultured rat pituitary alone does not respond to nicotine (Matta et al., 1987). These results clearly showed that the HPA axis is stimulated at a higher central nervous system level.

According to Rosecrans and Karin (1998) nicotine acts on central nicotinic acetylcholinergic receptors. As these receptors are widely distributed throughout the CNS, there are different pathways by which the HPA axis can be activated. Fuxe et al. (1989) provide a very detailed analysis of nicotinic receptor locations within the rat hypothalamus, describing three different receptor subtypes that may be effective in nicotine-induced HPA axis stimulation. Rat nicotinic receptors have been analyzed later on by the group of Fuxe with a focus on neuroprotective effects of nicotine (for a review Belluardo et al., 2000).

Matta et al. in contrast present data showing that nicotine does not directly stimulate the hypothalamic paraventricular nucleus (PVN). They showed using lesions and receptor blockade paradigms that brainstem noradrenergic regions, which project to the PVN play an important role in mediating the nicotine stimulation of the HPA axis. In detail, ACTH release was blocked by alpha1 and alpha2 adrenergic receptors in the hypothalamus. Specific brain stem regions appear to be the nucleus tractus solitarius (NTS) and to a lower extent ventromedullary regions, as activation in these region correlated with activation in the PVN as measured by cFos mRNA expression. Furthermore, a dose-dependent norepinephrine release after nicotine stimulation could be demonstrated in microdialysis experiments, which correlated with ACTH release (Matta et al., 1998). For a more in-depth analysis of the mechanisms, the excellent reviews by Fuxe et al. (1989), Rosecrans and Karin (1998), and Matta et al. (1998) are recommended.

With respect to the more chronic application of nicotine through cigarettes in human smokers' lives, the issue of desensitization has to be discussed. In rat studies, a rapid desensitization during sequential nicotine injections has been described. A single injection of 0.5 mg/kg nicotine was sufficient to completely abolish nicotine responsiveness one hour later (Sharp and Beyer, 1986). Hypothalamic cFos expression and norepinephrine release in the PVN (not in the periphery) was significantly reduced in response to repeated nicotine injections (Matta et al., 1995; Sharp and Matta, 1993). Matta et al. (1998) attributed the desensitization to a change in nicotinic acetylcholinergic receptors (Matta et al., 1998). Interestingly, as summarized above, the HPA axis in habitual cigarette smokers remains responsive to nicotine, if the dose exceeds a certain threshold, e.g., if the smoker smokes two cigarettes in short succession. It has to be taken into account, that in most human studies, smokers were studied after a non-smoking period of around one hour or in the morning, after a night without smoking. On the other hand, the reactivity of the HPA axis to other stimuli as psychosocial stress for example seems to be reduced (see below).

3. Altered basal activity of the HPA axis in habitual smokers

Given the strong activating effects of nicotine on the HPA axis, it could be assumed that smokers have higher cortisol levels throughout the day. Interestingly, many studies that explicitly set out to compare HPA axis hormones in plasma or urine between smokers and non-smokers were not able to detect any differences (Benowitz et al., 1984; Tucci and Sode, 1972; Yeh and Barbieri, 1989).

Kirschbaum et al. found elevated salivary cortisol levels in ten mainly female university students who smoked compared to ten non-smokers over a 12-h period. Saliva samples were obtained every 20 min during a day with regular lectures.

Interestingly, cortisol levels were significantly increased in smokers after each of the three major breaks during lectures, while no increases were found in non-smokers. It is therefore very probable that the increased mean cortisol levels may be attributed to these periods of high nicotine consumption. Cortisol levels during the rest of the day were rather similar between both groups (Kirschbaum et al., 1992). Concomitantly, Kirschbaum et al. were not able to replicate the findings of increased cortisol levels in another study using the same protocol with ten male non-smokers and ten smokers (Kirschbaum et al., 1994).

Smoking behavior was additionally assessed in a many studies looking at the cortisol response to awakening (CAR) and circadian profiles of cortisol. Here again, earlier studies did not find any significant differences (e.g., Pruessner et al., 1997). Steptoe and Ussher report an altered CAR in smokers together with a more comprehensive review of the literature (Steptoe and Ussher, this issue).

4. Altered HPA axis response to psychosocial stress in habitual smokers

In light of the significant desensitization of many central nicotine effects including HPA axis activation (Sharp and Beyer, 1986), it is remarkable, that smokers show high cortisol responses after smoking two cigarettes of the usual brand (e.g., Kirschbaum et al., 1992). Desensitization seems to occur towards other activating stimuli for the HPA axis, mainly for psychosocial stress.

In a first study, Tersman et al. did not find any significant differences in the HPA axis response to a mental arithmetic task between smokers and non-smokers in a mixed sex group (Tersman et al., 1991). This may be attributed to the fact that HPA axis activation per se may be low in response to a mental arithmetic task (Dickerson and Kemeny, 2004), that the sampling interval with just one sample after 15 min was not optimal to detect differences, or that the mixed-sex configuration may have lowered overall responsiveness.

Kirschbaum et al. compared effect of different stimuli for the HPA axis between ten male smokers and ten male non-smokers. All subjects were subjected to a saline injection, a hCRH injection, an exhaustive ergometry session, and a psychosocial stress test ("Trier Social Stress Test", TSST, Kirschbaum et al., 1993a). The HPA axis response to psychosocial stress was found blunted in smokers. Responses to the CRH test were slightly but non-significantly lower in smokers. Ergometry failed to induce a cortisol response in all subjects (Kirschbaum et al., 1993b). In a following study from the same laboratory, the protocol was modified in that plasma levels of cortisol and ACTH were additionally determined. Habitual smokers had lower salivary and plasma cortisol, as well as ACTH responses to psychosocial stress (only salivary cortisol reached statistical significance). Responses to CRH injection and exhaustive exercise were not significantly lower in smokers. However, since all measures were apparently slightly lower in smokers, the failure to reach significant was attributed to the small samples size of eleven smokers vs. eleven non-smokers (Kirschbaum et al., 1994).

No further studies have been published that addressed the issue of how smoking influences HPA axis responsiveness. In a recent study from our laboratory, we subjected 118 healthy university students to the TSST. Thirty-six of these participants reported to smoke a mean number of 10 cigarettes per day (SD: 6.38; range: 1 to 20). Mean age of the whole group was 22.2 years (SD: 2.1; range: 19 to 29 yrs.). Sixty-one of the participants were men, 57 were women, of the women 34 reported to use oral contraceptive medication.

As shown in Fig. 1, cortisol increased significantly in the whole group of subjects (ANOVA for repeated measures: time effect: F (1.37,156.67)=14.46; $p<0.0001$). In line with previous data, cortisol increases were significantly lower in women compared to men (sex by time effect: F (1.37,156.67)= 4.01; $p<0.04$). Smokers of both sexes displayed blunted cortisol responses as compared to same-sex non-smokers (smoking by time effect: F (1.37,156.67)=5.85; $p<0.01$). Sex and smoking behavior independently modulated cortisol responses (smoking by sex by time effect: F (1.37,156.67)= 0.22; $p=0.79$).

In summary, the data reviewed here together with recent results from our laboratory point to a blunted responsiveness

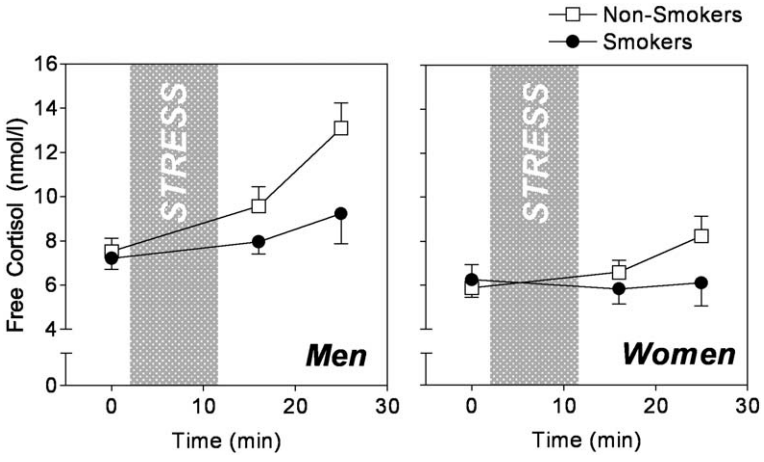

Fig. 1. Free cortisol response to the psychosocial stress test TSST (Trier Social Stress Test) in healthy young smokers and non-smokers.

of the HPA axis of habitual smokers to psychosocial stress. It is unclear so far how this decreased responsiveness is mediated. Whether this altered responsiveness has any negative health consequences, independent of the well-described negative consequences of cigarette smoking on the cardiovascular or respiratory system remains to be investigated. As the HPA axis plays an important role in the containment of inflammation (Munck et al., 1984), and a decreased HPA axis responsiveness has been implicated in the development or exacerbation of diseases associated with the inflammatory response (Buske-Kirschbaum et al., 2002), this may be an additional pathway leading to detrimental health outcomes in smokers.

5. Inflammatory activity in habitual smokers

That nicotine has profound effects on the immune system has been established in a large array of studies. We will not go into detail of these effects but focus instead on the release of inflammatory molecules. For a review of other changes in immune parameters in smokers, see for example (Sopori, 2002).

The inflammatory cascade is an important local response directed against invading pathogens and tissue damage (Tracey, 2002). Disinhibition of inflammatory mechanisms can lead to detrimental changes in the organism. Chronic low-grade inflammation has been implicated in the pathogenesis of atherosclerosis and thus is a potent risk factor of coronary heart disease (Ross, 1999). Since containment of inflammation is mediated in part by activation of the HPA axis (Munck et al., 1984), a decreased responsiveness as found in habitual smokers may foster disinhibition of inflammatory pathways and thereby contribute to cardiovascular morbidity and mortality in smokers.

5.1. Low-grade systemic inflammation in smokers

In fact, low-grade inflammation seems to be present in smokers as they are frequently found to have higher peripheral blood levels of inflammatory mediators. In a study investigating 880 healthy elderly subjects, Taaffe et al. reported increased circulating levels of interleukin-6 (IL-6) and C-reactive protein (CRP) (Taaffe et al., 2000). Increased CRP was also reported in a study with 2920 elderly men (Wannamethee et al., 2005), and in a study were more than 4000 smokers were compared to over 8000 never-smokers (Bazzano et al., 2003).

More specifically, cigarette smokers have more inflammatory cells (macrophages) and mediators (macrophage-derived metalloelastase/matrix metalloproteinase; MMP-12) in specimens of carotid vessel walls (Kangavari et al., 2004). Wirtz et al. investigated inflammatory processes in 41 healthy middle-aged habitual smokers compared to 52 non-smokers. In accordance with earlier results, smokers showed significantly increased plasma c-reactive protein (CRP) and a trend to increased tumor necrosis factor-alpha (TNF-α) levels. Interestingly, in vitro mitogen-stimulated release of TNF-α and IL-6 was significantly lower in smokers, and smokers' stimulated inflammatory response was more sensitive towards down-regulation by glucocorticoids (Wirtz et al., 2004). This is especially interesting as this finding of enhanced glucocorticoid sensitivity in peripheral blood is in contrast to the reports of decreased responsiveness of airway inflammation to therapeutic glucocorticoid treatment (see below).

5.2. Airway inflammation in smokers

In addition to low-grade systemic inflammation, one major complication of habitual smoking is airway inflammation, which may lead to chronic obstructive pulmonary disease (COPD). COPD is a disease characterized by progressive obstruction of the peripheral airways, associated with lung inflammation, emphysema and mucus hypersecretion (Groneberg and Chung, 2004; Perng et al., 2004). These inflammatory processes in the airways have recently been characterized in more detail. One important finding is that the transcription factor nuclear factor NF-kappaB (NF-κB) seems to be involved in the pathology of COPD. NF-κB is one of the central transcription factors of the inflammatory cascade, activating for example inflammatory mediators such as interleukin-1 (IL-1), IL-6, TNF-α and many more. Bronchial biopsies of both, healthy smokers and COPD patients, contained a significantly higher number of NF-κB positive cells, indicating a disinhibition of the inflammatory cascade (Di Stefano et al., 2002).

In contrast to the findings of an enhanced glucocorticoid sensitivity of whole blood stimulated cytokine production in smokers (see above, Wirtz et al., 2004), airway inflammation appears to display a relative glucocorticoid resistance. The mechanisms of glucocorticoid resistance have not been completely resolved, but overexpression of NF-κB as shown above, may be one of many alterations effective to decrease glucocorticoid responsiveness (Thomson et al., 2004).

5.3. Anti-inflammatory effects of nicotine

These findings have to be discussed in the light of at first sight contradictive evidence of anti-inflammatory properties of nicotine reported of in human and animal studies. Mills et al. for example showed a reduced experimentally induced skin inflammation after one month of transdermal nicotine treatment in life-long non-smokers (Mills et al., 1997). Animal studies using different modes of nicotine administration also show strong anti-inflammatory effects, such as impaired leukocyte migration to inflammatory sites (Razani-Boroujerdi et al., 2004), or in an experimentally induced inflammatory response (Kalra et al., 2004).

This apparent inconsistency of low-grade inflammation and airway inflammation on the one hand, and decreased responsiveness of the inflammatory system on the other hand, may be resolved by a hypothesis presented by Yun et al. (2005). According to their hypothesis, the detrimental effects of nicotine are not mediated by direct nicotine effects on target tissues, as they are, in fact anti-inflammatory, but by an imbalance of the autonomic nervous system, elicited by

frequent nicotinic stimulations (Yun et al., 2005). Whether this hypothesis will be able to explain all open questions of nicotine effects remains to be elucidated. However, the results of Wirtz et al. (2004, see above) are in line with his hypothesis, as they find a low-grade inflammation measured in peripheral blood, together with a decreased responsivity of inflammatory pathways in vitro.

6. Summary

As discussed in the sections above, the HPA axis of habitual cigarette smokers shows significant alterations compared to non-smokers. The main effective component of cigarette smoke on the HPA axis seems to be nicotine. Intravenous application of nicotine, as well as cigarette smoking, activates the HPA axis in habitual smokers, non-smokers and laboratory animals. Interestingly, while a desensitization of the HPA axis has been observed in animal studies and using intravenous nicotine application, the HPA axis remains highly responsive to cigarette smoking, even in persons who consume more than 20 cigarettes per day, given that a minimum number of two cigarettes is smoked in relatively short succession. Furthermore, much lower nicotine concentrations are necessary when delivered in tobacco smoke, as compared to other ways of application. This may point to the involvement of additional substances and/or involvement of other, presumably psychological processes, in HPA axis activation by cigarette smoking.

Despite these strong stimulating effects, many studies have reported only slight changes of basal HPA axis activity in habitual smokers. However, as Steptoe and Ussher report in this issue higher circadian levels and an increased awakening response, it may be that methodological shortcomings prevented earlier studies from finding these differences.

Another consequence of chronic cigarette smoking is a blunted HPA axis responsiveness to acute psychosocial stress, while responses to CRH injection or exhaustive exercise are not changed. This points to alterations in hypothalamic or higher CNS structures. While underlying mechanisms of these changes are unknown today, one can at least speculate about the consequence of blunted HPA axis responsiveness. As discussed above, the HPA axis has been implicated in the containment of inflammatory reactions, and a blunted responsiveness is associated with inflammatory diseases in animals and humans (e.g., Buske-Kirschbaum et al., 2002; Sternberg et al., 1989). Smokers do in fact show signs of low-grade systemic inflammation, and frequently develop chronic airway inflammation. Both conditions are associated with negative health outcomes and may be associated with altered HPA axis functioning.

However, as we discuss above, many issues remain unresolved so far, such as the discrepancy between anti-inflammatory effects of nicotine on the one hand, and inflammatory processes in smokers on the other hand, or increased glucocorticoid sensitivity in peripheral blood monocytes together with glucocorticoid resistance in airway tissues. Future studies will have to expand the knowledge reported here to a broader population. As summarized above, no data is available on how the HPA axis of the elderly responds to nicotine stimulation, whether psychosocial stress responsiveness, and whether the circadian pattern of cortisol is changed. This would be of special importance, as chronic low-grade inflammation is a typical complication of aging (Krabbe et al., 2004) and could be further stimulated by unfavorable changes of basal HPA axis activity. The same holds true for sex differences. Although many of the studies summarized here included women and men, it is not clear by now, if male and female smokers show different alterations of their HPA axes. Further tasks for the future will be the detailed characterization of the hypothesized interaction between peripheral inflammation and central HPA axis alteration in habitual smokers.

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