



Fatigue and stress reactivity are differently related to cigarette craving and hormone responses to neurotransmitter related drugs in nicotine deprived smokers



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ABSTRACT

Lack of drive in depression has been reported to derive from deficiency of dopamine, whereas high responsiveness of the noradrenergic and serotonergic system have been found to be associated with anxiety related components of depression. Since, furthermore, the three neurotransmitters and depression are relevant in smoking motivation, the present experiment investigates if fatigability (FA) and stress reactivity (SR), the two corresponding components of depressiveness measured as personality dimensions in the normal range, can be separated by drug induced hormone responses and cigarette craving and their combined effects.

Method: 36 Healthy male smokers assessed for FA and SR by questionnaires were tested under noradrenergic (NA), serotonergic (5-HT) and dopaminergic (DA) pharmacological stimulation in a placebo controlled balanced crossover design with respect to time and size of drug induced hormone responses and measures of cigarette craving during nicotine deprivation.

Results: Revealed that both FA and SR were related to early 5-HT responses but only FA showed late and low DA responses confirming the DA deficiency hypothesis. Smoking urge was increased by the noradrenergic drug merely in stress sensitive individuals, and larger prolactin responses to DA were associated with increased smoking urge. **Conclusions:** Facets of depressiveness can be discriminated by neurotransmitter related hormone responses. Personality related differences in motivation may be revealed by psychotropic drugs, and their underlying mechanisms may become evident by neurochemical responses to psychotropic drugs.

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1. Introduction

In the days of the foundation of the Journal "Personality and Individual Differences", a major focus in the study of individual differences was on the concept of arousal measured by parameters of the central nervous system, like EEG, as exemplified by the work of Robert Stelmack (e.g. Stelmack, 1990; Stelmack, Achorn, & Michaud, 1977) as well as by measures of the autonomic nervous system (e.g. Fahrenberg, 1969). By and large, approaches using neurochemical variables were introduced into psychophysiological research on individual differences. These were initiated by experiments in Pharmacopsychology, i.e. application of psychotropic drugs in order to detect personality related differences in emotional and performance responses to sedatives and stimulants (e.g. Janke, 1983). Furthermore, the application of pharmacological challenge tests derived from diagnostic tests in patients suffering from depression, anxiety or impulse control disorders (e.g. Kapitani et al., 1999) were introduced into research on individual differences in

personality. This latter approach was based on the concept that personality traits in the healthy population may be seen as the low end of a continuum into psychopathology and therefore might exhibit similar patterns of hormone responses to neurotransmitter related drugs.

Following this concept, the present experiment is based on findings that in depressed patients certain hormone responses are observed upon challenge tests with dopaminergic, serotonergic and noradrenergic drugs. Another clinical observation is that depressed patients tend to smoke more than respective healthy persons, and that depression is characterized by distinct facets of behavior, like pronounced sensitivity and reactivity to any kind of stressors on the one hand, as well as low energy and drive and the tendency to feel exhausted and tired, on the other, two facets, related to the concept of arousal. Therefore, the aim of the present experiment was to test, if depressiveness in the normal range can also be related to smoking urges and hormone responses to transmitter related drugs in the same way as in depressed patients, and, furthermore, if these features may be differently expressed in persons differently characterized by the two arousal related facets of depression, reactivity to stress and fatigability. Splitting of complex syndromes (depression) into specific phenotypes on the level of symptoms has received increasing interest in molecular genetic studies as well (see phenomics) and bears high potential for a better understanding of underlying biological mechanisms.

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1.1. Facets of depression

Clinical classifications according to subtypes of depression e.g. as anxious/agitated versus inhibited/apathic depression (e.g. Loew, 1965) has led to construct scales for the differentiation between the more anxiety related and the purely depressive aspects as e.g. in the Hamilton depression scale (Hamilton, 1976). This has led psychologists to verify these two aspects by factor analysis of psychometric tools (e.g. Clara, Cox, & Enns, 2001) and to include these aspects into the construction of personality test batteries (Cloninger, Przybeck, & Svrakic, 1991; Waller, Lilienfeld, Tellegen, & Lykken, 1991). So far, it is not clear, if biological correlates are different between the two subtypes.

1.2. Depression and transmitters

Since the early sixties deficits in the neurotransmitters serotonin and noradrenaline have been claimed to be related to affective disorders (Golden & Guilmore, 1990; Schildkraut, 1965), and therefore drugs for treatment of affective disorders had been developed to increase serotonin-, noradrenaline- and dopamine levels in the brain. Since levels of neurotransmitters or sensitivity of respective receptors in the brain cannot be measured directly in living humans, neurotransmitter challenge tests have been developed in Psychiatry for diagnostic as well as for therapeutic purposes. Disturbances in synthesis, release or degradation of the major neurotransmitters noradrenalin (NA), serotonin (5-hydroxy-tryptamine = 5-HT) and dopamine (DA) have been shown to be causally related to depression. Responsiveness of depressed patients to specific neurotransmitter related drugs may vary between patients. Indicators of responsiveness are levels of hormones in plasma, like cortisol, prolactin and growth hormone, due to effects of serotonergic, noradrenergic and dopaminergic drugs. They exert their effects by differences in release, transmitter reuptake activity into the presynaptic neuron by specific transporters, by sensitivity of pre- and postsynaptic receptors, or activity of transmitter metabolizing enzymes.

For deriving hypotheses concerning responses in healthy humans, it may be stated that.

Neurotransmitter challenge tests with serotonergic drugs revealed blunted cortisol responses to a 5-HT challenge test by D-fenfluramine (Cleare, Murray, & O'Keane, 1996; Newman, Shapira, & Lerer, 1998) possibly resulting from low production of 5-HT in depressed patients and in chronic fatigue syndrome (Dinan et al., 1997).

Noradrenergic stimulation with the NA related drug clonidine yielded high growth hormone responses in depressed patients (Charney et al., 1982; Lesch, Laux, Erb, Pfüller, & Beckmann, 1988) and high cortisol responses to reboxetine in healthy persons scoring high on a personality scale of depression (Hennig, Lange, Haag, Rohrmann, & Netter, 2000) were interpreted as indicating high receptor sensitivity due to low NA production.

Low prolactin responses to DA challenge tests were frequently reported in depressed patients (Hansenne et al., 2002; Pitchot, Ansseau, Moreno, Hansenne, & von Frenckell, 1992; Pitchot et al., 2001) and healthy depressive persons (Netter, 2006) due to low DA production.

In a previous study the onset of hormone responses to D-fenfluramine (a 5-HT-releaser), the challenge response was observed to occur earlier in high than in low depressive subjects (Netter & Reuter, 2005).

Therefore, **hypothesis 1** states that depressive healthy persons may show low and early serotonergic, high noradrenergic and low dopaminergic responses to respective challenge drugs.

So far, it has not been investigated, if transmitter challenge tests result in different patterns of hormone responses in persons of a more arousal related and more apathy/fatigue related type of depressiveness, but it could be expected that a) the noradrenergic system (related to arousal) will be more affected in persons of high stress sensitivity, and b) low dopamine activity related to lack of initiative and drive) would be more expressed in persons scoring high on fatigability.

1.3. Depression and smoking

There is not only a higher proportion of smokers among depressed patients than in healthy persons (Covey, Glassman, & Stetner, 1998), but the relapse rate after cessation of smoking is also correlated with levels of depression (Gilbert, Crauthers, Mooney, McClernon, & Jensen, 1999; Kinnunen, Doherty, Militello, & Garvey, 1996; Son, Markovitz, Winders, & Smith, 1997). Moreover, there are also higher levels of depressive symptoms, irritability and anxiety among healthy smokers (Haines, Imeson, & Meade, 1980).

Depending on the dose of nicotine and habituation of the individual, nicotine acts as an emotionally sedative as well as cognitive enhancing drug, and smoking is therefore used for reduction of stress as well as for increasing alertness and mental concentration (Russell, 1989). It was also tried to classify persons according to smoking motivation (Russell, Peto, & Patel, 1974), but a review on the relation between personality types and stimulation – versus sedation smoking (Lujic, Reuter, & Netter, 2005) revealed that the two motives are pronounced only slightly differently in anxious and depressive persons, but are both more frequently expressed in neurotic, anxious and depressive persons than in respective healthy groups.

Therefore **hypothesis 2** would predict that high scorers both on stress reactivity and fatigability will develop more cigarette craving upon deprivation from cigarettes than respective low scorers, but differences between the two types of high scorers cannot be predicted due to lack of respective studies.

1.4. Transmitter related drugs and cigarette craving

Since noradrenergic drugs induce physiological arousal similar to stress conditions, they may increase smoking urges, while serotonergic drugs might reduce cigarette craving due to their dampening effects on emotional arousal. With respect to dopaminergic drugs, it may be expected according to dopamine substitution theory (e.g. Le Foll, Schwartz, & Sokoloff, 2000) that they could serve as substitutes for dopamine release induced by nicotine, or they may stimulate smoking urges as predicted by the theory of incentive motivation (Robinson & Berridge, 1993). The latter was confirmed in healthy smokers in a study on smoking and dopaminergic drugs (Reuter, Netter, Toll, & Hennig, 2002). Transferring these findings to the two types of depressiveness, stress reactivity and fatigability, **hypothesis 3** would predict:

- Stimulation by a noradrenergic drug will increase craving particularly in high stress reactive depressives, because of their greater sensitivity to physiological arousal in stress conditions.
- Serotonergic stimulation will reduce craving more in depressive subjects in general based on the observation that depressed patients treated by specific serotonin reuptake inhibitors (SSRIs) smoke less than those treated by other drugs (Hughes, Stead, Hartmann-Boyce, Cahill, & Lancaster, 2014). But differences between the subtypes of depressiveness in healthy persons cannot be predicted.
- Due to their hypothesized low dopaminergic activity (hypothesis 1), persons high in fatigability should benefit more from dopaminergic stimulation according to the DA substitution theory and therefore develop less craving.

2. Method

2.1. Subjects

A sample of 36 male smokers (18–35 years, continuous cigarette consumption > 13/day for >4 weeks) selected according to a health questionnaire on a separate day participated in the experiment. Exclusion criteria were endocrinological, allergic, or cardiovascular diseases, previous or present neurological or psychiatric symptoms or

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