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Psychobiology of Sensation Seeking

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P. Netter[a]
J. Hennig[a]
I.S. Roed[b]

[a] Department of Psychology, University of Giessen,
[b] Bayer Pharma, Wuppertal, Germany

Serotonin and Dopamine as Mediators of Sensation Seeking Behavior

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Abstract
The purpose of the present paper was to investigate the relationship of the serotonergic and dopaminergic systems to subscales of sensation seeking (SS). Two of the subscales, Disinhibition (DIS) and Experience Seeking (ES), were chosen for analysis based on their representation of the two major factors obtained in a factor analysis: DIS represents a factor of lack of impulse control and ES a factor of novelty seeking. In studies 1 and 2 responsivity to a serotonergic (5-HT) challenge by a 5-HT_{1a} receptor agonist (ipsapirone) was investigated by drug-induced prolactin (PRL) and cortisol responses, as well as by emotional states and behavioral measures. The dopaminergic (DA) response to a DA agonist (lisuride) and antagonist (fluphenazine) was analyzed in a condition of smoking deprivation (study 3) using PRL responses, emotional states, and behavioral measures of nicotine craving as dependent variables. In the studies of the serotonergic system, high ES subjects showed a blunted cortisol response in both studies and high DIS subjects demonstrated a blunted PRL response in study 2. A frequently observed side effect of serotonergic agonists, increase in emotional arousal, was not observable with ipsapirone in high ES and high DIS subjects as compared to low scorers. Behavioral aggression, which had been experimentally induced in study 2, was increased in high ES as well as in high DIS by the 5-HT_{1a} agonist which exerted antiaggressive effects in low scorers. These findings were found compatible with the idea of a generally low responsivity of the serotonergic system in high ES as well as in high DIS types of sensation seekers or 5-HT_{1a} subsensitivity in high DIS and subsensitivity of other postsynaptic 5-HT receptors in high ES. There was no association between SS subscales and DA-induced decrease of PRL, but high ES subjects seemed to tolerate nicotine deprivation better than low ES subjects indicating that they were less susceptible to deprivation of nicotine-induced DA. But craving for nicotine was increased in high ES subjects by the DA agonist lisuride as opposed to the antagonist, which was taken as evidence that DA stimulation may induce approach behavior in high ES. Although only two subscales had been selected for the investigation, this approach suggests both common and different relationships between SS subscales and neurotransmitter systems.

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Prof. P. Netter, PhD, MD
Department of Psychology
University of Giessen
Otto-Behaghel-Strasse 10
D–35394 Giessen (Germany)

There is abundant literature relating personality disorders as defined by the psychiatric classification of DSM-III to deficiencies or abnormalities of the serotonergic system. After the first observation by Åsberg et al. [1] that suicide victims using the most violent methods had lower levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF), other kinds of deviant or aggressive behavior as observed in alcoholics, violent offenders, or drug addicts have been investigated with respect to serotonergic activity [2–5]. Challenge substances like the serotonin (5-HT) receptor agonist mCPP [3, 5, 6] as well as the releaser and uptake inhibitor dexfenfluramine [4] showed a blunted prolactin (PRL) response in groups of antisocial personality disorders, and some other studies yielded similar results for depressives with suicidality as compared to those without [3, 7, 8]. There are, however, also some studies which reveal an increased PRL response to dexfenfluramine [9] or no difference between the pathological and the healthy group [10]. The common denominator of the personality disorder investigated in this context was identified to be a lack of impulse control.

Although a continuum in behavioral abnormalities ranging from psychiatric states to normal personality characteristics has by now been widely accepted by psychologists and psychiatrists, it has not been widely confirmed that also the underlying neurotransmitter-related abnormalities represent a continuum from pathology to the normal range. If we conclude that impulsivity as a temperament trait may be the low end of a continuum, which at its high end is characterized by violent offense and impulsive abnormal personality disorders, we should expect that the same kind of abnormal responses in the serotonergic system will be observed in healthy subjects scoring high on a questionnaire of impulsivity. This has been investigated in a few studies by determination of 5-HIAA levels in the CSF [11] and by challenge tests trying to prove that personality dimensions related to impulsivity show similar abnormal responses as do patients with impulsive aggressive personality disorders [12–16].

The dopaminergic (DA) system is also related to aggression [17–20]. Infusion of DA agonists tended to increase isolation-induced fighting in rats, which could be reduced by destruction of DA neurons by 6-hydroxydopamine [21]. Furthermore, higher DA levels in the hypothalamus were observed in aggressive fighting rats [22]. Healthy human subjects have also been found to respond by anger to the application of the DA precursor *L*-dopa [23], and neuroleptics are known to be effective in reducing aggression in pathological states of aggression of different origins. Therefore extrapolation from pathological aggression to aggression in the normal range would predict a similar excess of DA activity in aggressive normal subjects. But DA has also been classified and identified as the transmitter associated with approach and reward [24] and therefore has been related to positive emotion sensu Tellegen [25], a trait related to extraversion and activity.

A personality dimension associated with all three groups of traits (impulsivity, aggression, and approach) described to be related to serotonin and DA is sensation seeking (SS) [26, 27]. Its four subscales: thrill and adventure seeking (TAS), experience seeking (ES), disinhibition (DIS), and boredom susceptibility (BS) load on a second order personality factor of unsocialized impulsive SS [28]. Although Zuckerman et al. [29] show that SS and aggression are orthogonal factors in a 5-factor model, both SS and aggression load on a psychoticism (P) factor in a 3-factor model, and therefore the type of aggression represented by ignoring social norms as measured by DIS would justify linking SS to the aggression-related DA system. Furthermore, SS also represents the behavior of approach and reward seeking which is described as being dominated by the DA system [24, 30, 31]. So the biochemical model developed by Zuckerman [26] relating SS to the neurotransmitters would predict that high SS exhibit high DA, low serotonin, and low norepinephrine values. In this respect the Zuckerman model deviates from Cloninger's [32] idea that single motives like harm avoidance and novelty seeking relate to single transmitters like serotonin and DA respectively.

So far hardly any studies have been performed using drugs as research tools in order to prove the relationship of neutrotransmitters to SS.

In the present paper only the DA and 5-HT systems will be addressed. Since many clinical studies could successfully prove that hormone responses (PRL, cortisol, growth hormone) to neurotransmitter challenge tests are suitable tools for investigating sensitivity of 5-HT and DA receptors, the studies reported here will be restricted to those in which hormone responses were available.

Although the four SS subscales certainly share a large proportion of common variance, it seems worthwhile to analyze subscales instead of the total score with respect to their relation to the 5-HT and DA systems, since in some previous studies only isolated subscales revealed a relationship to the transmitters [33–35].

Since most of the studies in the pathological range related neurotransmitter-based research to impulsivity, aggression, and psychopathy, the first question to address is: (1) How are the subscales of SS associated with mea-

sures of impulsivity, aggression, and psychoticism (P-scale)? In a second step we have to analyze: (2) What is the relationship of (a) the serotonergic and (b) the DA system to the SS subscales? The methodology for question 2 will be dealt with in the respective sections.

Relationships between SS Scales and Impulsivity, Aggression, and the Psychoticism Dimension

Table 1 shows the results of a factor analysis obtained on 224 male students relating the four subscales of SS to impulsivity as measured by the impulsivity-venturesomeness-empathy scale [36], the aggression scale of the Freiburg Personality Inventory (FPI, scale 6) [37], and the psychoticism scale (P-scale) of the Eysenck Personality Questionnaire [38].

As shown in table 1, the 2-factor solution as well as the 3-factor solution yield evidence that the scales TAS and ES form a separate factor, whereas the other two scales, DIS and BS, either form a common factor with aggression and impulsivity or divide fairly equally into an aggression-impulsivity factor and a psychoticism factor. The results differ from those in other factor-analytic studies [28, 29], in which ES had higher loadings on the overall PImpUSS factor (psychopathy – impulsive unsocialized sensation seeking) than DIS and was less related to TAS than in our study. Yet it is justified to select ES and DIS as representatives of two different aspects of SS for neurotransmitter-related analyses in this paper. ES best taps into the broad genetic factor common to all subscales, and DIS has more significant biological correlates than the other scales, whereas TAS is highly culture-loaded, and BS is the least reliable scale [26].

Relationships of the SS Scales to the Serotonergic System

Two studies will be presented in which cortisol and PRL responses to the serotonergic challenge by a 5-HT_{1a} receptor agonist were assessed in combination with psychological measures. Previous studies in which only performance or emotional states had been taken as indicators of serotonergic responsivity [15, 35] will be omitted.

Table 1. Two- and three-factor matrices and respective eigenvalues and percent variance (%) in a sample of n = 224 male students

	Two-factor solution		Three-factor solution		
	FI	FII	FI	FII	FIII
TAS	0.038	**0.825**	0.178	–0.178	**0.826**
ES	0.175	**0.783**	–0.013	0.281	**0.779**
DIS	**0.654**	0.430	0.414	**0.521**	0.419
BS	**0.754**	0.034	0.402	**0.668**	0.020
IMP	**0.764**	0.207	**0.729**	0.352	0.197
Agg	**0.633**	0.039	**0.875**	0.013	0.034
P	**0.586**	0.084	–0.009	**0.847**	0.070
Eigenvalues	2.76	1.12	2.76	1.12	0.93
Variance, %	39.4	16.0	39.4	16.0	13.3

IMP = Impulsivity; Agg = aggression; P = psychoticism. Bold type = substantial factor loadings (>0.50).

Method

In *study 1*, SS subscales were analyzed with respect to their relation to cortisol, PRL, and emotional responses to the 5-HT_{1a} agonist ipsapirone as compared to placebo.

20 healthy male students were assigned to either the placebo or the ipsapirone group. At 3 p.m. subjects had a catheter inserted into the vein of their left forearm, which was connected to a plastic tube leading outside the chamber, so that blood samples could be drawn unnoticed by the subjects. 45 min after insertion of the cannula identical capsules of either placebo or 10 mg of ipsapirone were administered, and 55, 90, and 110 min after intake of the drug blood samples were drawn. At the time of blood sampling and at about 15-min time intervals saliva specimens were obtained by salivettes.

Salivary cortisol was determined by radioimmunoassay according to the procedure suggested by Kirschbaum et al. [39], and plasma PRL was analyzed by radioimmunoassay as well. Emotional states were assessed by an abbreviated version of the adjective checklist developed by Janke and Debus [40]. The dimensions relevant to serotonin were emotional arousal, anger, alertness, activity. Data were analyzed by three-way analyses of covariance with the baseline values as covariates in the SS subscales divided at the median into high and low scorers as well as the drug condition (ipsapirone vs. placebo) as group factors.

Since 5-HT_{1a} agonists have been claimed to have antiaggressive properties [41], *study 2* compared the effects of ipsapirone to placebo in an aggression-inducing condition in 40 healthy males randomly assigned to an aggression induction or a control condition with 10 subjects each tested under placebo and under ipsapirone. Aggression was induced by a competitive modified Master Mind game and a provocative accomplice of the experimenter who had to apply loud noise to the subject as a punishment for wrong guesses. Furthermore, the subject lost money to the accomplice who was made to win twice within eight sets of trials. In the control condition the instruction was given that this game was just a pilot study testing how guesses would turn out in this Master Mind game. Furthermore, the accomplice behaved in a friendly manner, and no subtraction of money followed after losing the game.

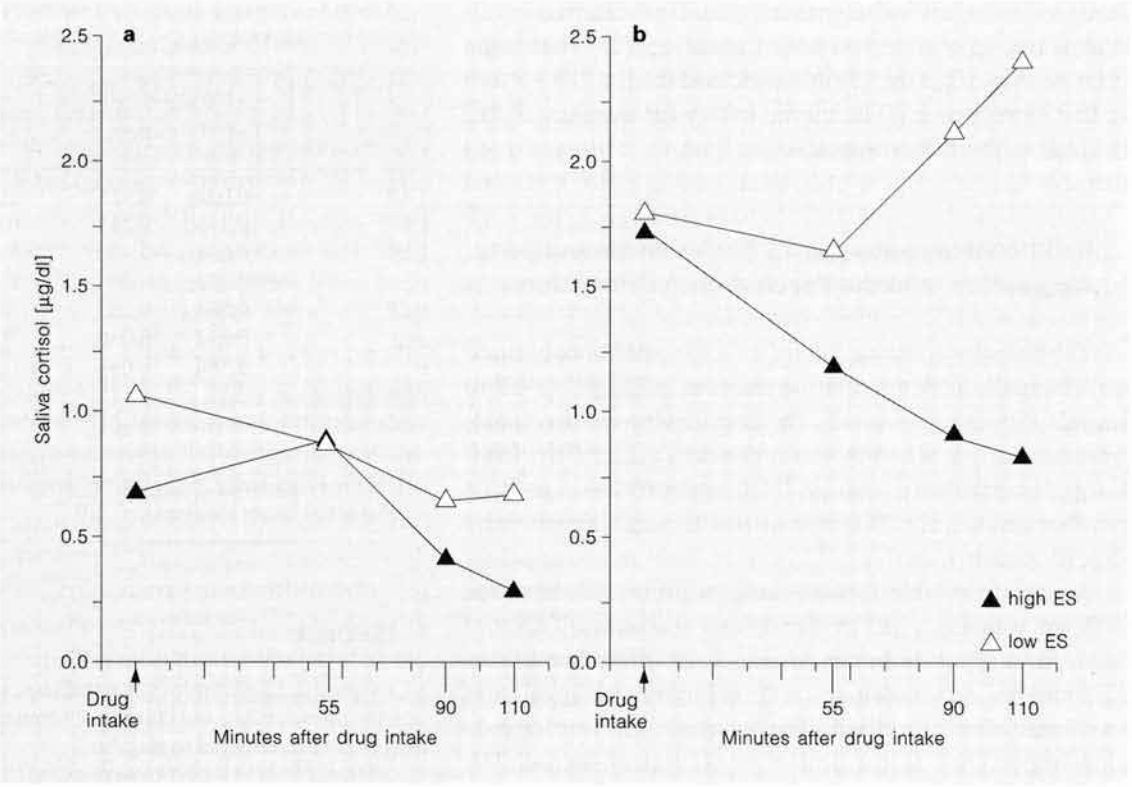

Fig. 1. Study 1. Cortisol response in the placebo (**a**) and ipsapirone (**b**) group in high and low ES. Drug effect. $F = 12.46$, d.f. = 1, 32, $p = 0.001$; ES effect: $F = 6.21$, d.f. = 1, 32, $p = 0.018$; interaction drug × ES: $F = 2.51$, d.f. = 1, 32, $p = 0.123$.

Ipsapirone was applied in a single oral dose of 10 mg before instruction on the game, at which time the subject was first confronted with the accomplice. Blood samples were drawn for determination of PRL at baseline, after the instruction, after the game, and 20 min later in order to allow measurements of readaptation to baseline. At the same time saliva samples were obtained by salivettes for measuring cortisol, and questionnaires were applied for ratings of the preceding situation (questionnaire constructed for this particular study), and ratings of the accomplice after the instruction and after the game (semantic differential of 25 adjectives to be scored on a 7-point scale each). Furthermore, intensity and duration of noise applied to the accomplice for each pair of wrong guesses by the subject were used as behavioral measures of aggression.

Factor analyses were computed for the ratings of the preceding situation and for the accomplice ratings yielding a factor of nonspecific emotional arousal and of aggression for ratings of the experimental situations as well as a factor of aggression in the accomplice ratings which will be used for the present analysis.

For statistical evaluation, analyses of covariance for repeated measures were computed in the total group, and in both the aggression induction and the control group separately with the factors drug (ipsapirone/placebo), SS score (high/low), and experimental phase with the additional factor condition (Aggr./control) in the total group. These analyses were performed for the scales personality factors DIS and ES separately.

It is clear, of course, that the study has only a pilot character due to the low number of cases in each group (5/5 and 6/4 according to post hoc median formation).

Results

Study 1. When analyzing cortisol effects as responses to the 5-HT_{1a} agonist ipsapirone in high and low ES subjects, the expected increase in cortisol induced by ipsapirone turns out to be exhibited only in low ES subjects, whereas the high ES subjects are significantly lower throughout (fig. 1) and less responsive to ipsapirone (there are, however, only main effects of the drug and of ES and only an interaction at the level of $p = 0.12$). The DIS scale did not yield any influence on cortisol responses, nor was there any association between PRL levels and responses with the SS dimensions ES or DIS.

Since 5-HT agonists are known to reduce alertness and activation as well as anxiety, these scales were also analyzed. Clear drug by time interactions were observable ($F = 4.63$, d.f. = 2, 72, $p = 0.013$) indicating larger deacti-

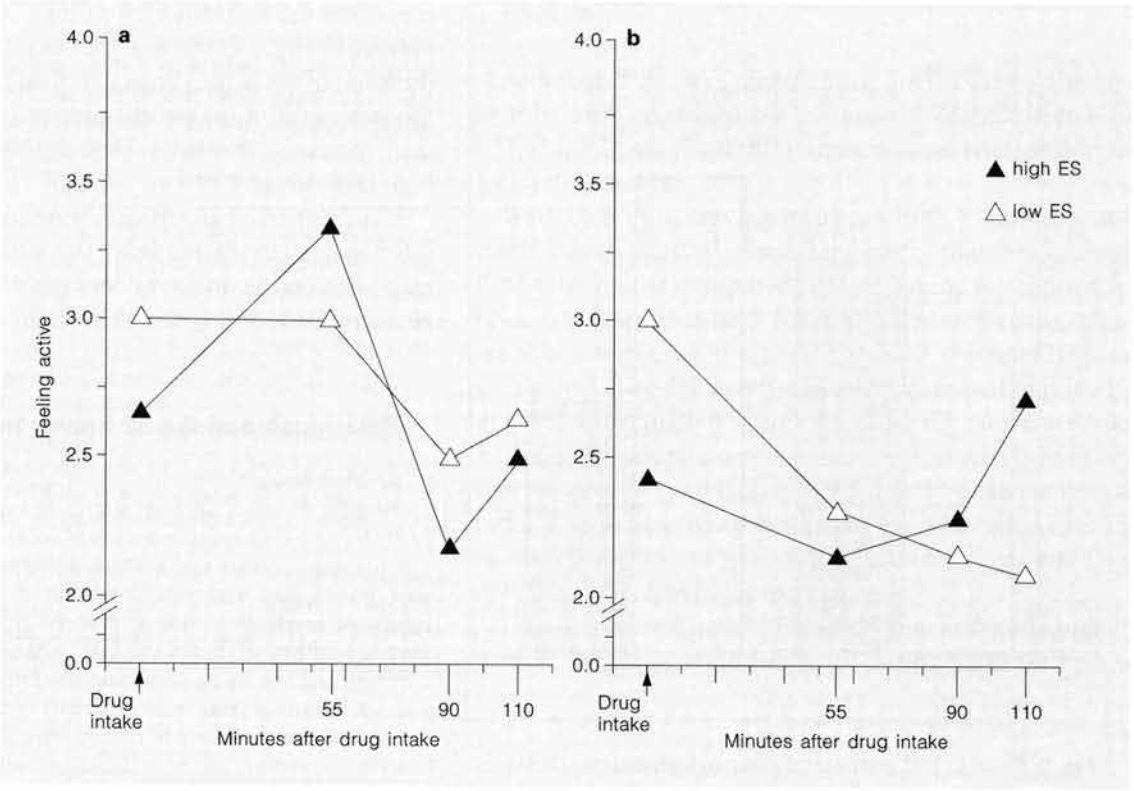

Fig. 2. Study 1. Ratings on activation in the placebo (**a**) and ipsapirone (**b**) group in high and low ES. Time effect: $F = 3.83$, d.f. = 2, 72, $p = 0.026$; drug × time: $F = 4.63$, d.f. = 2, 72, $p = 0.013$; drug × ES × time: $F = 2.42$, d.f. = 2, 72, $p = 0.096$.

vating drug effects at the peak time if ipsapirone and a reactivation under placebo at the end of the session, which was not observed with ipsapirone. The interaction of drug by time by ES, however, was only close to significant ($p = 0.096$). As can be seen from figure 2, high ES subjects developed a reactivation under ipsapirone, which was not the case in low ES subjects.

Study 2. Analyzing hormone responses in study 2 in the total group as well as in the aggression induction and control groups separately yielded the following results: Cortisol responses only showed a significant drug by time by ES interaction in the control group ($p = 5.30$, d.f. = 2, 30, $p = 0.011$), whereas the subscale DIS did not reveal any relationships with cortisol responses. High ES subjects had lower cortisol responses to the 5-HT_{1a} agonist than low ES replicating the findings of study 1. Under conditions of aggression induction the effect was no longer observable.

With PRL as the dependent variable there was no influence observable for ES, but an interaction in the total group with the DIS scale ($F = 4.56$, d.f. = 1, 30, $p = 0.041$), which could not be reproduced in the separate analyses of the aggression induction and control groups. As depicted in figure 3, a blunted response to ipsapirone was observed in high as compared to low DIS subjects.

Comparing subscales with respect to ipsapirone-induced antiaggressive effects on *emotions and behavior* the results were as follows: In the total group given placebo, situations were rated as more arousing by high ES as well as by high DIS subjects as compared to the respective low scorers, but given ipsapirone low ES as well as low DIS subjects responded by higher feelings of emotional arousal. The respective high scorers, however, gave about the same ratings under the 5-HT_{1a} agonist as with placebo (fig. 4). The interaction obtained in the total group could also be observed in the aggression induction condition for the DIS scale ($F = 4.09$, d.f. = 1, 15, $p = 0.041$), but not for the ES scale indicating a true effect of ipsapirone on reduction of aggression-induced emotional arousal only for high DIS subjects.

As to drug effects on *behavior*, on opposite effect emerged: Ipsapirone seemed to reduce aggressive behav-

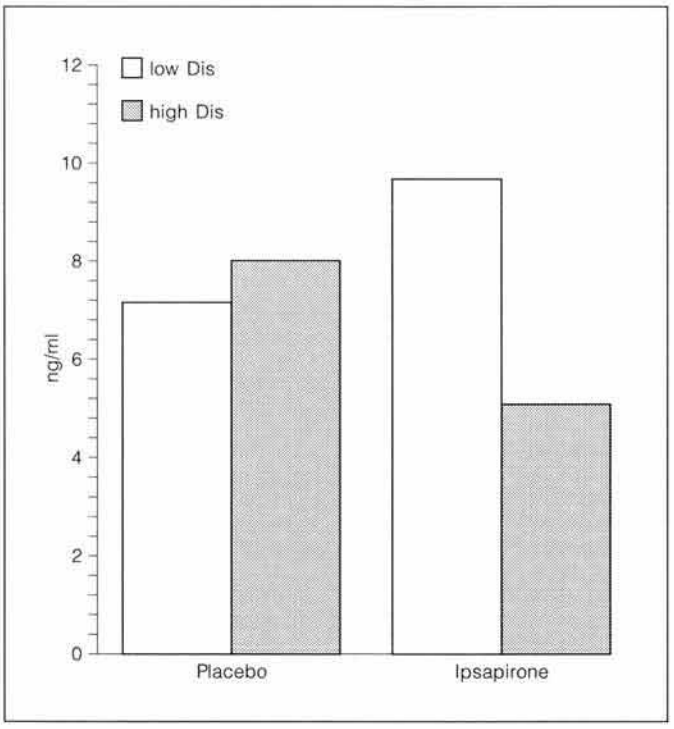

Fig. 3. Study 2. PRL in the total group in high and low DIS (average across measurements 2, 3, 4, after instruction, after the game, and end of session). Analysis of covariance: Interaction drug × DIS: F = 4.56, d.f. = 1, 30, p = 0.041.

ior in low ES as shown by ratings of the confederate as aggressive (fig. 5a) and low DIS as indicated by a reduced duration of noise the subject applied to the confederate by the push button for wrong guesses (fig. 5b), whereas the drug increased this behavioral aggression in high ES and high DIS subjects.

Unfortunately, group sizes were too small to allow correlational analyses between the drug-induced hormone responses on the one hand and emotional and behavioral changes elicited by ipsapirone on the other.

Relationship of the SS Scales to the DA System

Method: Study 3

Because nicotine has been shown to exert its rewarding effects partly by release of mesolimbic DA [42–44], the effects of a DA agonist (0.2 mg lisuride) and a D_1D_2 antagonist (2 mg fluphenazine) were investigated under the condition of smoking deprivation as compared to placebo using a balanced crossover design. Subjects were 36 healthy male heavy smokers (>20 cigarettes per day) divided into high and low ES and high and low DIS subjects on the SS subscales. Cigarette craving was assessed by three measures:

(1) Different amounts of money were displayed in randomized order on a computer screen to the subject who had to decide for each amount of money if he rather preferred a cigarette or the money displayed. Subjects were instructed that the subject's choice at one of the 30 trials was randomly selected by a computer program and executed

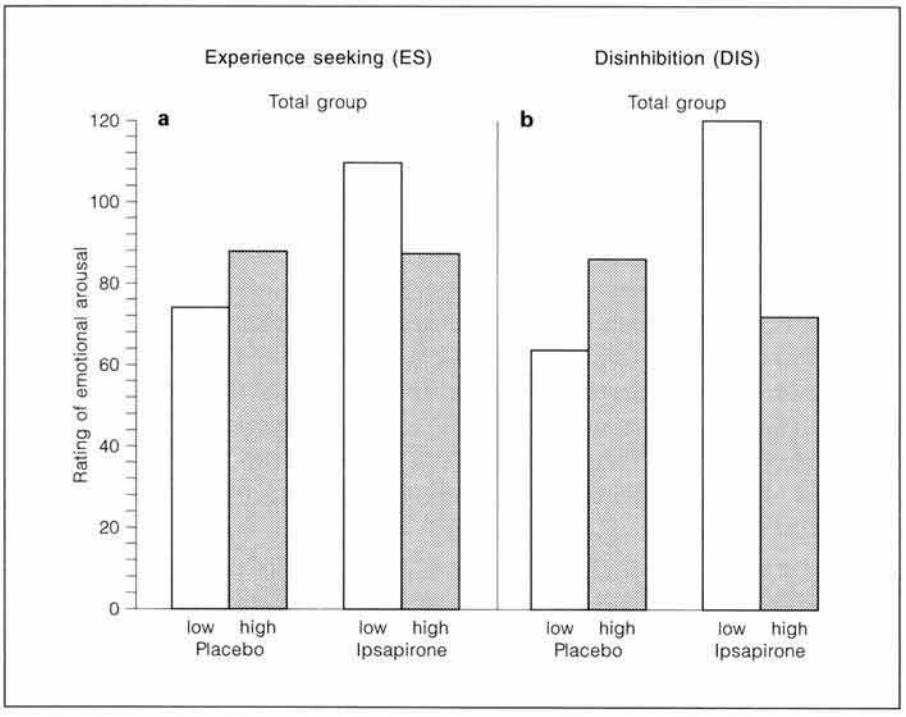

Fig. 4. Study 2. Factor scores for rating the situation as emotionally arousing (average across three time points of the experiment) according to high and low scorers on ES (**a**) and DIS (**b**) under placebo and ipsapirone in the total group. Interaction drug × ES: F = 3.16, d.f. = 1, 30, p = 0.085; interaction drug × DIS: F = 4.47, d.f. = 1, 30, p = 0.043.

by offering either a cigarette or the respective amount of money chosen by the subject at that particular trial. The computer was manipulated so that one of the choices in which money had been preferred to the cigarette by the subject was executed in the baseline run, and a cigarette choice was selected at the end of 2.5 h of smoking deprivation.

(2) A rating scale on the desire for smoking was applied.

(3) A preference scale was administered comparing a number of activities like walking, reading, social activities, etc. with smoking a cigarette. These activities had been rated before according to the degree to which they were liked by the subject, so that only highly liked activities could be selected on the basis of their previous ratings compared with the desire for smoking a cigarette. The score was an average across the ratings, if a cigarette was less, equally, or more desirable than the best liked activities.

Due to the PRL inhibiting effects of DA, PRL is increased by DA antagonists and decreased by agonists. Therefore blood samples were drawn for determination of PRL as an indicator of DA responsivity from an indwelling catheter at baseline and 2.5 h after smoking the last cigarette.

Furthermore, subjective ratings on well-being and activation were obtained. Analyses of covariance were performed with a repeated measures factor of drug (agonist/antagonist/placebo) tested at 1-week intervals in a balanced order with baselines serving as covariates.

Results

Although PRL was significantly increased by the antagonist and decreased by the agonist (drug effect $F = 9.71$, d.f. = 2, 48, $p < 0.001$), there was no relationship to the SS dimensions.

With respect to craving measures high ES subjects tolerated being deprived of smoking better than low ones as illustrated by the computer choice craving test shown in figure 6a. The same held for high DIS subjects as compared to low ones ($F = 4.52$, d.f. = 1, 30, $p = 0.042$) [data not shown]. The DA agonist lisuride increased craving in high ES and actually lowered it in low ES subjects, while the antagonist fluphenazine took an intermediate position between placebo and lisuride (indicated by the change of preference for smoking compared to other activities in fig. 6b). There was no relationship between drugs and DIS with respect to craving responses.

For high ES but not for high DIS a significantly higher increase of general wellbeing after fluphenazine and a

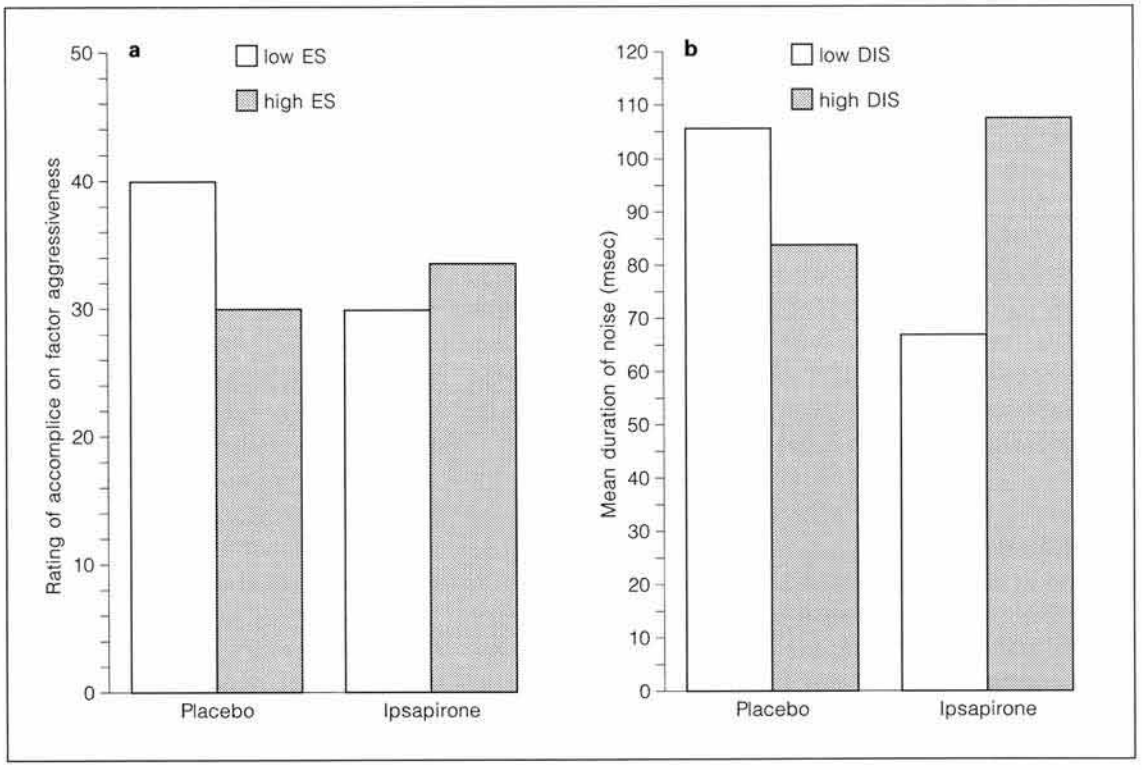

Fig. 5. Study 2. Behavioral measures according to high and low SS scorers under placebo and ipsapirone in the aggression induction condition. **a** ES: rating of accomplice. **b** DIS: mean duration of noise button pressing to punish the accomplice for wrong guesses. Interaction drug × ES: $F = 3.39$, d.f. = 1, 15, $p = 0.086$; interaction drug × DIS: $F = 7.01$, d.f. = 1, 16, $p = 0.017$.

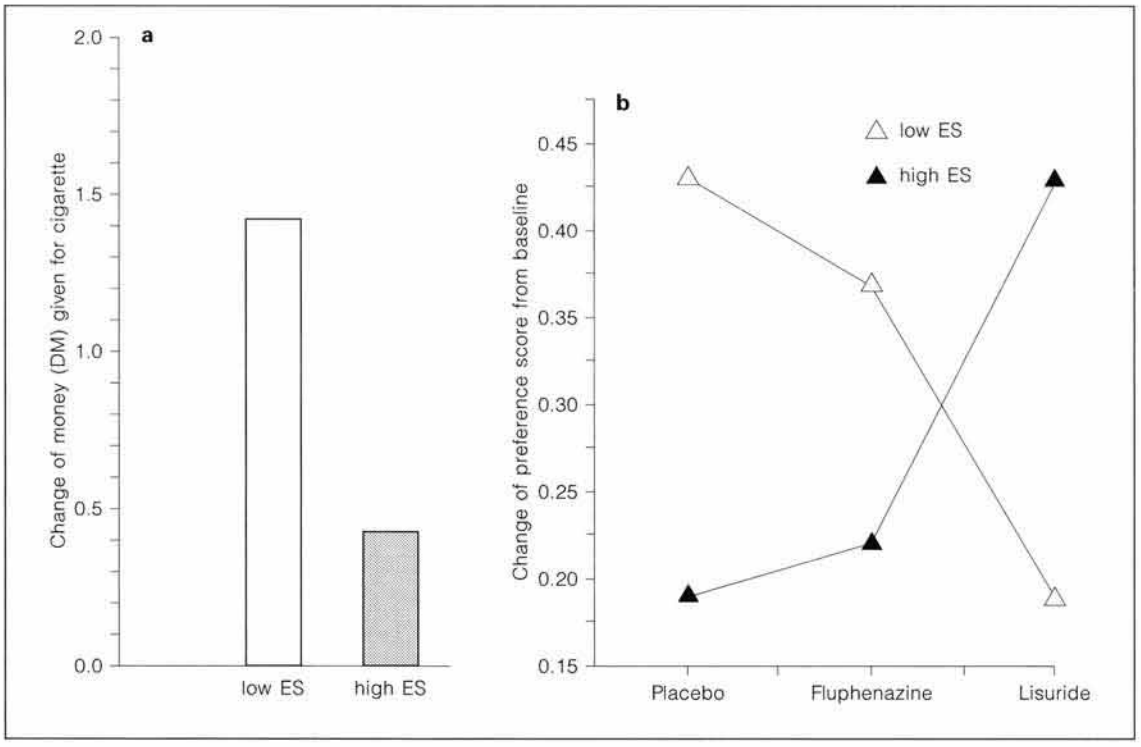

Fig. 6. Study 3. **a** Craving after 2.5 h of smoking deprivation in high and low ES (computer choice: amount of money sacrificed for cigarette after deprivation as compared to baseline). ES effect: $F = 9.80$, d.f. = 1, 30, $p = 0.004$. **b** Changes of craving for a cigarette in high and low ES (end of deprivation minus baseline score) measured as preference of smoking to certain activities (average across 16 items) according to drug interaction drug × ES: $F = 4.80$, d.f. = 2, 62, $p = 0.011$.

decrease after lisuride as compared to low scorers was observed after nicotine deprivation ($F = 3.14$, d.f. = 2, 63, $p = 0.05$). For DIS a close to significant interaction with the drug factor was observed for emotional irritability (with lisuride: decrease in low DIS, no change in high DIS; with fluphenazine no change in low DIS, slight decrease in high DIS, $F = 2.88$, d.f. = 2, 63, $p = 0.064$).

Discussion

Studies 1 as well as 2 seem to indicate that ipsapirone-induced cortisol responses are blunted or absent in high ES as compared to low ones, but they do not seem to be related to the dimension of DIS.

This may become more meaningful when comparing ipsapirone-induced cortisol responses to other personality variables in study 1. High responses had been observed in highly impulsive subjects [45] and were correlated in study 1 with irritability and aggression (FPI-R scales [37], $r = 0.531$, $p = 0.019$, $r = 0.526$, $p = 0.021$, respectively). Low responses were not only correlated with ES but also with contentedness with life, extraversion (FPI scales, $r = -0.448$, $p = 0.054$ and $r = -0.391$, $p = 0.098$, respectively), and the coping style of minimization of the stressor [46] ($r = -0.481$, $p = 0.037$). These correlations indicate that ES evidently reflects the opposite of irritable aggression and shares common variance with a positive stress-resistant attitude towards life. If we follow Coccarro's [47] line of reasoning that a constantly low serotonergic transmission may (a) lead to upregulation of postsynaptic and/or subsensitivity of presynaptic 5-HT_{1a} receptors and (b) to a lowering of the threshold of sensitivity to aversive stimuli with the consequence of increased hypersensitivity and hyperirritability, then the increased cortisol responses to the 5-HT_{1a} agonist in subjects with high trait aggression and irritability could be plausibly related to their low 5-HT activity. The opposite would hold true for high ES subjects (high 5-HT transmission, subsensitive postsynaptic receptors, low cortisol response; this must not be

mistaken for the blunted cortisol response observed in depressives [48–50], which is interpreted as a reduced responsivity of the HPA axis similar to nonsuppression of cortisol by the dexamethasone inhibition test in depressed patients).

Disinhibition has evidently too little in common with the positive traits mentioned above to follow the same pattern as ES and therefore was not related to cortisol at all in studies 1 and 2.

Although the PRL response is observed in many other 5-HT_{1a} agonistic substances (mCPP, buspirone, fenfluramine), its relevance to the 5-HT challenge with ipsapirone has been discussed controversially [51]. Since in our study 1 there was a significant ipsapirone-induced increase in PRL in the total group ($F = 5.63$, d.f. = 1, 32, $p = 0.024$), it seemed justified to use it as an indicator of individual differences in 5-HT reactivity. However, this hormone did not seem to be differently affected in subjects divided according to high and low DIS or ES in study 1. However, in study 2, possibly due to the stressful condition of the game, high DIS subjects showed the blunted PRL response which has been reported for highly impulsive subjects in several studies using the 5-HT releaser and uptake inhibitor fenfluramine [24, 47].

So far it has not yet been clarified why cortisol and PRL responses are not only differently related to different 5-HT agonists [47, 51], but are also characteristic of partly different aspects of personality [16].

Differences in mechanisms of release may be responsible for the differences in PRL and cortisol response, since fenfluramine-induced PRL – but not cortisol – responses could be antagonized by the 5-HT_{1a} antagonist pindolol [52]. But it is probably too premature to conlcude, on the basis of the present pilot study, that the dimension of ES (being more responsive to cortisol) is related to postsynaptic 5-HT receptors other than 5-HT_{1a}, said to be responsible for cortisol release [53], whereas DIS, although only in study 2, would be related more specifically to abnormalities of 5-HT_{1a} receptors held responsible for PRL release [52].

The blunted cortisol response of high ES in study 1 is accompanied by less drug-induced deactivation in high than in low ES subjects which could indicate lower responsivity to the deactivating properties of the 5-HT agonist. In study 2 high ES also respond by less ipsapirone-induced irritability than low ES subjects. (Transient paradoxical increases in irritability are reported as side effects of several 5-HT agonistic drugs [54, 55] and may be due to presynaptic stimulation of 5-HT_{1a} receptors by the drug (reduced 5-HT release and thereby more feelings of irritable aggression). The phenomenon of reduced ipsapirone-induced irritability is also observed in high DIS as compared to low DIS subjects in study 2, where it parallels the blunted PRL response of high DIS subjects. If the expected response upon 5-HT challenge is a transient increase in irritability, the reduction of emotional arousal in high ES as well as in high DIS again reflects their lower 5-HT responsivity.

Furthermore, reduced emotional arousal in study 2 was paralleled by ipsapirone-induced increases in aggressive behavior in high ES as well as in high DIS subjects indicating again a lack of responsiveness to the antiaggressive effect of the drug.

With respect to the dopaminergic system it was surprising that neither of the two subscales of SS tested showed a relationship to PRL responses upon the DA agonist and antagonist clearly observable in the total group. Therefore two questions arise: Either we may not have chosen the right subscales of SS or there may be only a responsivity at the psychological level as shown by differences in drug-induced modification of cigarette craving. As to the first hypothesis, it has indeed been shown by previous evaluations using DA agonists and antagonists that the dimension of BS showed the closest relationships to DA. This was demonstrated by lower performance decrements and more favorable emotional responses in high BS subjects given the DA antagonist haloperidol and less favorable ones to the DA precursor *L*-dopa as compared to low BS subjects [35]. In a clinical setting Wiesbeck et al. [33] showed that alcoholics scoring high on BS responded by higher growth hormone responses to the DA agonist apomorphine than those low on BS. Both findings correspond to behavioral observations obtained in apomorphine-susceptible rats [56] indicating that evidently higher levels of DA or lower DA receptor sensitivities in highly novelty seeking subjects may be hypothesized.

Therefore an additional analysis was performed with BS in study 3 with respect to PRL responses as well as to psychological associations with dopaminergic drug effects. Surprisingly, no such associations were observed for PRL or craving. This could, of course, be due to the fact that a low potent neuroleptic used as an anxiolytic (fluphenazine) was applied as opposed to the much more potent drug haloperidol, which caused considerable side effects at a dosage of 3 mg [35]. Furthermore, effects on craving may not be related to those on performance.

Further additional analyses of the BS dimension yielded evidence that the antagonist F did not decrease wellbeing in high as opposed to low BS, and that lisuride, the agonist, had a beneficial effect on motivation for per-

formance in low as opposed to high scorers ($F = 3.71$, d.f. $= 2, 63$, $p = 0.003$, and $F = 2.55$, d.f. $= 2, 63$, $p = 0.086$ respectively for the interaction drug × BS). There seems to be a tendency for BS to reflect the results obtained in the previous study [35] at least on the subjective level.

The other hypothesis, that effects may only be observed on a psychological and not on a hormone response level, could be supported by the fact that high ES subjects exhibited less craving than low ES subjects possibly on the basis of their higher levels of DA. The effect of the drugs on this deprivation period shows that fluphenazine, the antagonist, indeed did not affect high as much as low ES subjects, which would be in line with the previous observation obtained for BS. The fact that lisuride, the agonist, increased craving considerably in high ES (fig. 6b) might either mean that presynaptic stimulation of DA receptors is responsible (reduced DA release) or that DA agonists do not only act by substituting a lack of DA in the brain but also trigger the pleasurable sensation evoked by certain stimuli as postulated by Robinson and Berridge [57], which would imply that these hedonistic aspects of DA are more pronounced in high than in low ES.

Since ES is associated with a positive view of life and novelty seeking (see above), its responsivity to DA stimulation fits the DA-induced PRL responses reported by Depue [24] as characteristics of the personality dimensions related to novelty seeking. Positive emotion (which Depue claims to correspond to extraversion) was seen as the dimension most responsive to DA challenge, whereas negative emotions like irritability and aggression turned out to be most responsive to PRL release upon serotonergic challenge. In this respect ES and DIS results obtained in our studies will fit these findings if we consider DIS as more related to irritable impulsivity and ES more to novelty seeking. Depue claims that this aspect of novelty seeking must be associated with actions for obtaining positive goals, whereas the serotonergic PRL responsivity is associated with premature actions which are not related to reinforcing goals. This may explain why BS, which is also associated with novelty seeking but perhaps not as much with undertaking actions as ES, does not show the craving response to DA challenge which has been observed for ES in study 3.

The idea that novelty seeking has really a basis in genetic abnormalities of the DA receptor has recently been confirmed by genetic studies [58]. It could be shown that subjects carrying the 7 allele of the D4 receptor had higher scores in novelty seeking than those with the normal genotype. It is probably a subject for future research in molecular genetics to discover which aspects of personality and behavior can also be attributed to genetically controlled variations in serotonergic and noradrenergic receptors.

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