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Short Communication

Responsiveness to A Serotonergic Drug is Characteristic for Impulsivity-Related Food Craving in Healthy Humans

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• Impulsivity; Eating (disorder); Transmitter sensitivity; Serotonin; Dopamine

Abstract

The questions investigated were, if the association between serotonergic transmitter sensitivity and food craving in combination with addiction related personality traits can be identified by a drug challenge test in healthy persons, and if dopamine has an additional role. In a fourfold placebo controlled balanced crossover experiment on healthy male individuals hormone responses to a serotonin (5-HT) reuptake inhibitor and a Dopamine (DA) agonist and questionnaire based impulsivity scores were analyzed with respect to development of desire for eating.

Results: Revealed that only persons exhibiting high serotonergic responses and high motor impulsivity developed more desire for eating in the 5-HT condition. The same was observed for low DA responsiveness of high motor impulsives in the DA condition.

Conclusions: Healthy persons representing addiction related personality traits may show similar transmitter responses reported for addicted patients. Low 5-HT and high DA-activity inferred from the response patterns in high motor impulsive persons are associated with the development of desire for eating. Therefore, effects of serotonergic responsiveness on addictive behavior should be investigated considering specific addiction related personality traits and additional effects of dopaminergic activity in the same individuals. Results may disclose hidden propensities for the development of addictions.

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) has been shown to be associated with major psychiatric diseases like depression [1,2], schizophrenia [3] and addictive disorders [4,5], but also with psychopathological symptoms associated with aggression and impulsivity [6,7]. This has been demonstrated to be not only valid in patients, but also in healthy humans exhibiting these traits in a milder form [8]. The relationship of 5-HT to impulsivity and aggression in healthy persons has for instance been demonstrated by 5-HT depletion experiments [9], as well as by experiments testing responsiveness of the serotonergic system by drugs like 5-HT reuptake inhibitors or releasers [10]. Impulsivity has been shown to be significantly correlated with addictive behaviors, as nicotine and alcohol dependence [11-13]. In the pathological range, in particular food craving in eating disorders has been found to be associated with low levels or low output of 5-HT [14,15].

However,

-since any symptom and behavior or temperament trait has been shown to be mediated by several transmitters acting in combination [16,17].

-since furthermore, interference with the serotonergic system often affects the dopaminergic and noradrenergic systems as well [18], and

-since addictive behavior due to its relation to reward, has particularly been found to be related to dopaminergic activity [19,20], responsiveness to serotonin related traits and behaviors should be investigated in combination with responses to additional transmitters, in particular with dopamine responses

Therefore, the questions addressed in the present study are:

1) Is the normal desire for eating, i.e. developing hunger and appetite, also related to serotonin in healthy persons?

2) Can impulsivity be found to be a moderating

personality trait in this relationship also in healthy persons?

3) Can similar relationships of hunger and appetite be observed with dopamine sensitivity?

METHOD

Assessment of responsiveness and procedure

Measurement of brain- derived transmitters is not reliably possible by measuring respective plasma levels, since most transmitters are also produced in peripheral glands or the gut. Therefore, transmitter responsiveness, assessed by hormone responses to respective transmitter specific drug challenges, was chosen as an indirect methodological approach:

In a fourfold placebo controlled balanced crossover experiment, 36 healthy males (20-35 years) were exposed to **Drug challenges** at one week intervals with 30mg of the specific 5-HT-reuptake inhibitor citalopram, 1,25 mg of the D2 receptor Dopamine (DA) agonist bromocriptine, 4 mg of the specific Noradrenaline (NA) reuptake inhibitor reboxetine, Placebo.

Hormone responses were measured between 2 and 7 pm in plasma obtained from an indwelling catheter at 10 time points each session and questionnaires for assessment of present affective states and hunger/ desire for food were filled in after the start with a standard meal of 400 calories and at the end of each session.

Responses were defined as baseline subtracted and placebo corrected positive peaks of *cortisol responses* to challenges with citalopram (for 5-HT) and reboxetine (for NA) indicating increase of 5-HT or NA activity and negative peaks of *prolactin(PRL) decrease responses* to the DA agonist indicating increase of DA activity.

Analysis of noradrenergic responsiveness was not included into the present study

Assessment of impulsivity traits and desire for eating

BIS 11 Impulsiveness Scale [21], 30 items , subscales Motor, Cognitive and Nonplanning Impulsivity, 10 items each scored on a 4 point Lickert scale; only Motor and Cognitive Impulsivity were selected because of their representation of hyperactivity Attention Deficit Syndrome (ADHS) type impulsivity

Scale of actual affective states [22], 15 Items scored on a 5 point Lickert scale; selected item "feeling hungry"

Scale of actual activity preferences: [22] 15 Items, scored on a 5 point Lickert scale; selected item: "eating sweet food"

Statistical Procedures

Responses were used as independent variables by dichotomy at the median of the hormone response scores into high and low responders. Two-factorial analyses of variance were performed with the variables: Response to transmitter (high vs low), Motor Impulsivity (high vs low) or Cognitive impulsivity (high-vs low) respectively, and with the dependent variables: Scores on hunger and desire for sweet food respectively.

RESULTS

Serotonergic stimulation by the specific 5-HT reuptake inhibitor citalopram did not increase hunger or desire for sweet food during 4 1/2 hours of the session as compared to the placebo condition in the total group. (p >.05). There was also no difference in placebo corrected cortisol responses to citalopram between high and low motor impulsives or between high and low cognitive impulsives (p>.05 each). However, the interaction in the two factor analysis of variance revealed: Only persons high in Motor Impulsivity and exhibiting high cortisol responses to the serotonergic stimulation developed a significant increase in hunger during 4 ½ hours of the session (p=.044) as shown in fig1 left, while the interaction between serotonergic cortisol response and Cognitive Impulsivity was not significant (Figure 1 right, p>.05)

A special evaluation with respect to the item "desire for sweet food" confirmed this phenomenon in an even more pronounced way: Persons scoring high in Motor

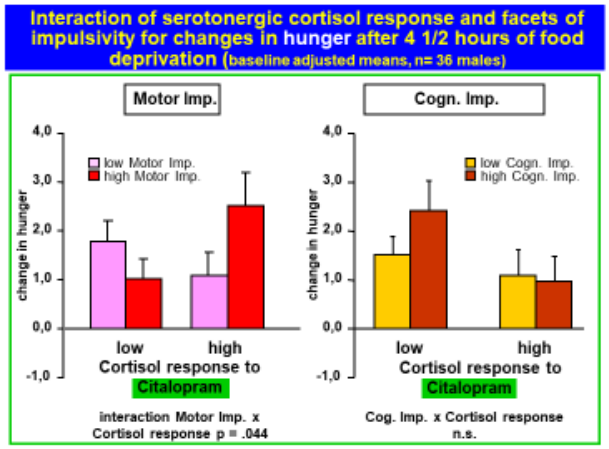


Figure 1 Combined effects of placebo corrected cortisol responses to citalopram (high vs. low) and Motor Impulsivity (left) and for Cognitive impulsivity respectively (right) on the development of hunger during 4 1/2 hours of the experimental session (n.s. p>.05).

Impulsivity and showing high serotonergic responses developed a stronger desire for sweet food than low scorers (Figure 2 right, p=.011).

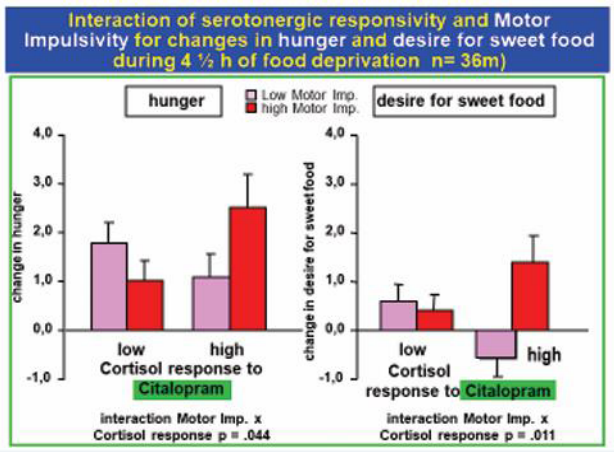


Figure 2 Combined effects of placebo corrected cortisol responses to citalopram and Motor Impulsivity on hunger (left, see Fig 1) and on desire for sweet food (right) during 4 ½ hours of the experimental session.

Since the 5-HT reuptake inhibitor may also slightly act on dopamine D2 receptors in the tuberoinfundibular system [18-23], dopaminergic sensitivity was also tested by the dopamine challenge with bromocriptine.

Corresponding analyses of variance with high vs low PRL responses to bromocriptine and high vs low impulsivity scores revealed that participants characterized by high Motor Impulsivity and low DA responses to bromocriptine were the ones who developed more hunger (p=.024,), while no significant effect was observed for those with high Cognitive Impulsivity and low PRL responses (p>.05, Figure 3). The same was observed for desire for sweet food (not shown).

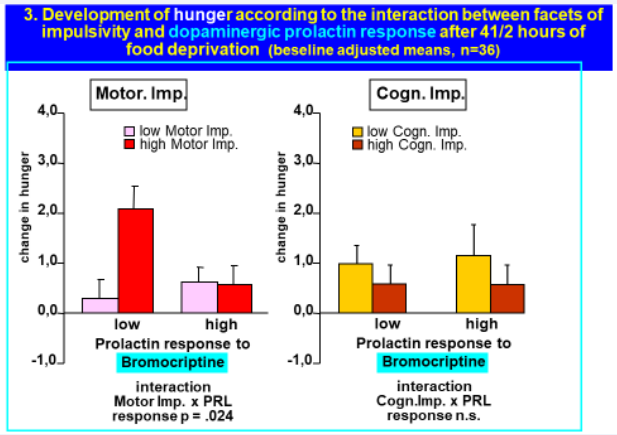


Figure 3 Combined effects of placebo corrected prolactin responses to bromocriptine(high vs.low) and Motor Impulsivity (left) and for Cognitive Impulsivity respectively (right) on the development of hunger during 4 ½ hours of the experimental session,(ns p>.05)

DISCUSSION

Results seem to indicate that healthy persons who exhibit the kind of impulsivity which mirrors hyperactivity in patients with ADHS and who are additionally characterized by high sensitivity of the serotonergic system, may develop more desire for eating, in particular for sweet food. This may result from an upregulation of 5-HT receptors as a consequence of low 5-HT production or release as described for bulimics [14,15], and patients suffering from impulse control disorders [24]. Motor Impulsivity is significantly correlated with questionnaire scores on aggression and with addictive smoking, (p<.001, each), while Cognitive Impulsivity, defined by attention deficits, shows no significant relationship with addiction and aggression [25]. Therefore, a (probably latent) disposition for low 5-HT levels or release in persons high in motor impulsivity (a behavior trait associated with aggression and addiction) may be the underlying condition, which, upon stimulation of the serotonergic system by a 5-HT agonistic challenge, may result in developing the desire for eating [26].

The relation of impulsivity to dopamine responses may be explained by the close relationship of high dopamine activity reported for addiction as well as for aggression and impulsivity in patients and in controls [19-27]. The blunted decrease of PRL upon stimulation by the agonist indicates less DA responsiveness in high motor impulsive individuals when stimulated by the DA agonist. This may be due to downregulated receptors following constantly high DA activity reported for aggression. The motivational response of developing more hunger and desire for sweet food reflects the affinity of DA to addictive and reward related behavior [19], which has also been demonstrated for cigarette craving in nicotine deprived smokers as well [28].

So, in summary, the results indicate that high motor impulsives characterized by high responsiveness of the serotonergic system and low responsiveness of the dopaminergic system may exhibit addiction related behaviors, when challenged by respective transmitter specific drugs. This may give rise to the hypothesis that the combined effect of low serotonin and high dopamine transmitter activity in persons of high motor impulsivity may reveal a hidden disposition for the development of addictive disorders.

CONCLUSIONS

1. Healthy persons representing addiction related personality traits may show similar transmitter responses reported for patients

2. 5-HT transmitter responses in combination with an addiction related personality trait may reveal a far better association between serotonergic activity and addictive behavior than the serotonergic drug alone.

3. The administration of a dopamine challenge in addition to a 5-HT drug challenge assessed in the same individuals characterizes more specifically the underlying transmitter activities associated with food craving than investigations based on a single transmitter

Moreover, the study is suitable to demonstrate a promising approach by using biological responses as independent variables in psychobiological studies.

LIMITATIONS

-The study is only based on a small sample of only young males. The small homogenous sample was, of course, the consequence of having to perform a fourfold crossover with single participant sessions.

- Hormone responses may not only indicate levels of transmitter activity induced by the drug , but also e.g. the reactivity of the affected hormone system, counter-regulatory processes of other hormones or peptides, genetically determined number of receptors, metabolic and emotional states of the individual and many more non-controlled variables.

-Questionnaire scores on eating variables are only represented by single items

Yet the study can demonstrate that drug challenge tests, as partly applied in psychiatry for predicting therapeutic response, can also be applied as useful diagnostic research tools in subclinical populations.

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