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Neuroendocrine correlates of temperamental traits in humans

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Abstract

Studies investigating temperament traits in humans and their biological correlates have found high levels of novelty seeking (NS) linked with dopaminergic system changes, and particularly a deficit of dopamine transporter. Harm avoidance and reward dependence, on the other hand, appeared to be associated, respectively with serotonin and noradrenaline changes. In the present study, we have investigated the dopaminergic (DA), serotonergic (5-HT), and noradrenergic (NE) functions in healthy volunteers by challenging the monoamine systems with the DA agonist bromocriptine, the 5-HT agonist D-fenfluramine, and the NE agonist clonidine, respectively. Parallel to this investigation, we examined the temperament traits of our subjects by measuring NS, harm avoidance (HA) and reward dependence (RD) using the 'Three-dimensional Personality Questionnaire' (TPQ). The aims of the study were to see whether or not the monoamine functions were correlated with temperament traits. Bromocriptine challenge induced a significant GH increase and a significant suppression of PRL. D-fenfluramine test significantly increased PRL and cortisol plasma levels and Clonidine test induced a significant rise in GH values. NS scores showed a significant direct correlation with brom-stimulated GH values (r=0.426, $P<0.05$) and a significant inverse correlation with brom-inhibited PRL values (r=−0.498, $P<0.01$). HA scores correlated significantly with D-fen-stimulated PRL and CORT AUCs, (PRL: r=0.424, $P<0.05$; CORT: r=0.595, $P<0.005$). RD scores correlated positively with clon-stimulated GH values (r=0.55; F=8.6; $P<0.01$) and negatively with brom-inhibited-

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PRL AUCs ($r=-0.439$, $P<0.05$). Our data support Cloninger theory concerning the biological correlates of temperamental traits, and evidence the link between the neuroendocrine responses to dynamic challenges and stable temperament features.

Keywords: Novelty seeking; Harm avoidance; Reward dependence; Dopamine; Serotonin; Noradrenaline; Growth hormone; Cortisol; Prolactin; Bromocriptine; Clonidine; D-fenfluramine

1. Introduction

The biological basis of personality dimensions has been repeatedly sought with contradictory results: temperamental traits appear to be associated with biochemical brain changes and genetic correlates also in animal studies (Angio et al., 1988; Walker et al., 1989; Giorgi et al., 1994; Dellu et al., 1996; Siegel and Driscoll, 1996).

The dimensions of human temperament proposed by the Cloninger model (1994) are defined as those components of personality that are heritable, developmentally stable, emotionally based, uninfluenced by sociocultural learning, and linked to specific brain biological features as revealed by genetic, neuroanatomic, neurophysiological studies. They include novelty-sensation seeking (NS), harm avoidance (HA), and reward dependance (RD) (Goldsmith et al., 1987; Cloninger et al., 1993; Cloninger, 1995; Menza et al., 1995; George et al., 1996).

Novelty seeking (NS) is a personality dimension defined as a compulsive need for varied, novel and complex sensations with the willingness to take physical and social risks for the sake of such experience. The sensitivity to only emotional overstimulation seems to be due to a higher arousal threshold (Zuckerman, 1996). It has been suggested that mesolimbic and mesofrontal dopaminergic (DA) projections might be involved in incentive activation of NS. Experimental evidence suggests that this character could be genetically determined and, in particular, could be associated with the DRD4*7R allele at the D4 dopamine-receptor locus (Cloninger, 1987; Bardo et al., 1996; Benjamin et al., 1996; Cloninger et al., 1996; Ebstein et al., 1996; Gelernter et al., 1997; Kotler et al., 1997; Noble et al., 1998). According to Cloninger (1987) and Ruegg et al. (1997), NS correlates positively with density of the dopamine transporter responsible for the presynaptic reuptake of dopamine, higher levels of NS being linked to reduced DA release from presynaptic neurons and compensatory increased sensitivity of postsynaptic DA receptors. In contrast, the data of Netter et al. (1996) and Zuckerman (1994) suggest that novelty seekers have high dopamine and low serotonin (5-HT) functions.

HA, or behavioral inhibition, seems to be associated with 5-HT function, high HA scores being related to high 5-HT release from presynaptic neurons and with postsynaptic 5-HT receptor down-regulation. Alterations of the serotonin transporter gene have been found involved in the biological impairments underlying HA alterations (Ruegg et al., 1997). More recent studies suggest a linkage between a functional polymorphism in the promoter of the human serotonin transporter gene and

two anxiety-related subdimensions of harm avoidance (Mazzanti et al., 1998), anxiety-related traits in adults (Katsuragi et al., 1999) and harm avoidance in an elderly population (Ricketts et al., 1998).

RD is associated with the formation of conditioned signals of reward (Corr et al., 1995). This temperament trait seems to be linked to norepinephrine function, low levels of urinary 3-methoxy-4-hydroxy-phenylglycol (MHPG) having been reported in subjects with high RD, while a supersensitivity of alpha-2-adrenoceptors, deriving from decreased NE secretion, has been observed in low RD individuals (Garvey et al., 1996; Ruegg et al., 1997; Cloninger, 1998).

Data on central norepinephrine (NE) secretion and activity in novelty seeking subjects are also contradictory. There was a negative correlation between NS scores and concentrations of NE and its main metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in the cerebrospinal fluid (CSF) and plasma, both in normal subjects and in pathological condition (Angio et al., 1988; Zuckerman and Cloninger, 1996). However, increased NE tone with higher than normal MHPG values in CSF but lower than normal plasma have been reported in pathological gamblers and in patients with NS combat related posttraumatic stress disorder (Ballenger et al., 1983; Siever et al., 1987; Arque et al., 1988; Zuckerman, 1994). Finally, in normal individual no correlations were also observed between plasma concentrations of MHPG and NS (Angio et al., 1988).

In a recent study we found a positive correlation between NS scores measured with the Cloninger Three-dimensional Personality Questionnaire (TPQ) and norepinephrine (NE), prolactin (PRL), and testosterone (Te) baseline plasma levels in healthy subjects (Gerra et al., 1999). Our data were in agreement with those of the literature for NE, T and PRL secretion patterns (Daitzman et al., 1978; Johansson et al., 1979; Daitzman and Zuckerman, 1980; Roy et al., 1988; Dabbs et al., 1991; Siever and Davis, 1991; Joyce et al., 1994; Wang et al., 1997), while they contrast with those of Ballenger et al. (1983), Arque et al. (1988) and Zuckerman (1990, 1994), who reported a negative correlation between central and peripheral concentrations of NE, MHPG, cortisol and NS scores.

The aim of the present study was to see whether or not the neurotransmitter and hormonal alterations correlate with specific temperament traits, in agreement with Cloninger theory. The central monoamine functions were indirectly evaluated by measuring hormonal responses to pharmacological challenges acting on central pre- and postsynaptic receptors specific for NE, DA, and 5-HT functions.

The DA function was investigated by the growth hormone (GH) and prolactin (PRL) responses to acute administration of bromocriptine (a specific D-2 receptor agonist): GH rise after bromocriptine seems to be stimulated by the dopaminergic system influencing, with neurons from nucleus arcuatus and nucleus paraventricularis, the hypothalamic secretion of GH-releasing hormone (GH-RH) (Muller et al., 1984); the suppression of PRL induced by bromocriptine may be related with a more peripheral dopaminergic action on tubero-infundibular system (TIDA).

The 5-HT function was evaluated by the PRL and cortisol (CORT) responses to acute stimulation with D-fenfluramine (a specific 5-HT releaser and agonist): hormonal increases may be interpreted as the expression of the specific involvement of

different 5-HT receptors systems; in fact, 5-HT1A receptor seems to be involved in the control of PRL secretion, but not of cortisol secretion (Palazidou et al., 1995); on the other hand, cortisol secretion stimulated by 5-HT agonist may occur following 5-HT2C stimulation, in the presence of 5-HT1A receptor blockade (Meltzer and Maes, 1995).

NE function was measured by the GH responses to acute stimulation with clonidine (an alpha-2-adrenergic agonist): GH rise after clonidine challenge would measure the sensitivity of postsynaptic noradrenergic receptors, as a possible compensatory response to presynaptic noradrenergic changes, but does not directly investigate presynaptic NE secretion.

In parallel, in the same individuals we investigated the temperament traits with the Cloninger TPQ.

2. Methods

2.1. Subjects

Twenty-two healthy male volunteers, recruited from the hospital staff (20–32 years; M±SE: 27.1±6.1), participated in the study. After complete description of the study to the subjects, written informed consent was obtained. All the subjects were caucasians; they were university students (9), nurses (4), hospital workers (9); no one had financial difficulties or other stressful life events at the time of the study; 13 out from 22 were living with the parents; nine subjects were married from some years; no psychiatric symptoms were found in the history of the participants. These volunteers have been reported as controls for other studies, in comparison with substance abusers (unpublished data).

Exclusion criteria included severe chronic liver or renal diseases or other chronic physical disorders, recent weight loss or obesity, endocrinopathies, neurologic disorders, immunopathies, and, in particular, HIV disease. Transaminases (GOT, GPT), liver function indexes, creatinine clearance, basal hormonal levels, white cells subpopulations, ECG and EEG measures were found in the normal range in all the participants. Neurologic objective evaluation did not found signs of central nervous system diseases.

The psychiatric assessment, described in the specific section, permitted to exclude axis I and II disorders at the time of the study. Possible psychopathologies or deviant behavior in the history were investigated and excluded, utilizing a semi-structured interview with the participants, and a double interview with their parents to avoid symptoms denial. Furthermore all the volunteers were well known by the authors from many years. Personal knowledge of the authors and the double interview with the parents of the participants permitted to exclude previous use of psychoactive drugs, substance abuse and dependence in the history of the subjects.

All the participants presented a negative history for family psychiatric disorders.

Volunteers were controlled by urinary drug screening for 4 weeks before the study and immediately before (2 h) the experimental days, to exclude substance abuse.

They also abstained from smoke or caffeinated beverages 7 days before the biochemical investigations.

2.2. Temperament and psychiatric assessments

All the subjects were submitted to a structured interview and a diagnostic evaluation by a trained psychiatrist, utilizing the SCID (Structural Clinical Interview) for axis I disorders (Spitzer et al., 1990, Italian Version: Clinical Interview structured for the DSM-III-R by Fava et al., 1993) and the SIDP (Structured Interview for DSM IV Personality Disorders) for axis II disorders (Pfohl et al., 1989: Italian Version by Maggini and Piccini, 1994): interrater reliability coefficients were 0.65 and 0.58, respectively for axis I and II (Cohen kappa).

No one of the participants showed the criteria for axis I or II psychopathologies. Personality disorders and other psychopathologies were also assessed by the Minnesota Multiphasic Personality Inventory II (MMPI II) (Hathaway and McKinley, 1995), and possible depressive trait was measured by the Hamilton Rating Scale for Depression (HRS-D, 21 items). The temperament traits of the subjects were studied clinically and with psychometric measures. NS, RD, and HA were measured by the TPQ (Cloninger, 1987). The Vocabulary and Digit Symbol subtest from the Wechsler Adult Intelligence Scale (WAIS and WAIS-R) (Wechsler 1955, 1985) and the Category Test (Reitan and Wolfson, 1993) were used to evaluate cognitive capacities.

2.3. Neuroendocrine challenges

All the participants were off any medication for at least 2 months before the study. They consumed a low monoamine diet and avoided smoking during the 7 days prior to the neuroendocrine tests, which were done at the day hospital of our Institute after an overnight fast and 1 h of bed-rest, in recumbent position. The three neuroendocrine challenges (i.v. clonidine test, oral D-fenfluramine test, and oral bromocriptine test) were administered 4 days apart one from the other (day 1, day 6, day 11)

The clonidine (Clon) challenge started at 09:00 h, on day 1, with an intravenous catheter inserted in an antecubital vein, kept patent by saline infusion. At 10:00 h, 2 ug/kg b.w. of clon (Catapresan-Boehringer, Italy) diluted into 10 ml of saline were injected as a bolus. Blood specimen for GH assays were drawn into EDTA-containing tubes immediately before the clon injection, and 15, 30, 45, 60 and 90 min afterwards. Blood was immediately centrifuged, and plasma stored at −20°C until assayed. The D-fenfluramine (D-fen) challenge started at 08:00 h on day 6 with an indwelling catheter inserted into a forearm vein, kept patent by saline infusion. EDTA-treated blood samples for PRL and cortisol assays were obtained at 08:30 and 08:45 h (times=−15 and 0). D-fen hydrochloride, 30 mg (Glipolix, Stroder-Italy), was administered orally at 08:45 h and blood specimen were drawn 30, 60, 90, 120, 180 and 240 min later and immediately centrifuged, and plasma frozen at −20°C

until assayed. The bromocriptine (brom) challenge was done on day 11, with a catheter inserted at 09:00 h into an antecubital vein, kept patent by saline infusion. At 10:00 h, 5 mg of brom (Parlodel, Sandoz, Italy) were administered orally. Blood specimen for GH and PRL assays were drawn into EDTA-containing tubes immediately before the brom administration, and 15, 30, 60, 90 and 120 min afterwards. Blood was immediately centrifuged, and plasma stored at −20°C until assayed. GH and PRL concentrations were measured radioimmunologically with the commercial kits of Sorin (Italy).

The sensitivity of the method for GH was 0.5 ng/ml and for PRL 1 ng/ml; the inter-assay variability for GH was 7.3% and the intra-assay variability 4.9%; and for PRL inter-assay variability was 4% and intra-assay 7%. CORT concentrations were measured radioimmunologically with the Boehringer-Mannheim kits. The sensitivity of the methods was 1 ng/ml; inter-assay and intra-assay variations were 3.7 and 7.5%.

2.4. Statistical analyses

The consistency of the distribution of the sample with the normal hypothesis was tested calculating the reduced χ^2 and determining the associated probability (Korn and Korn, 1968): the data distribution was normal.

The statistical analyses included the Student's *t*-test, the analysis of variance (ANOVA) with and without repeated measures, the multifactorial ANOVA, the analysis of covariance (ANCOVA), and the stepwise multiple regression analysis where appropriate. The relationship between the measures of temperament and personality traits (i.e. the subscales scores of TPQ and the MMPI) and of the areas under curves (AUCs) of PRL and CORT responses to the D-fen stimulations, of GH and PRL responses to the brom stimulation, and of GH responses to the clon stimulations were tested by the Pearson's correlation analysis.

3. Results

3.1. Temperament traits assessment

TPQ analysis showed NS mean scores=16.5±0.9; RD mean scores=17.6±1.2 and HA mean scores=19.4±1.1. TPQ values were in the normal range for healthy subjects, accordingly with the standard levels suggested by Cloninger manual (Cloninger et al., 1994). Our volunteers showed a great inter-individual variability of MMPI 2 scores and Hamilton scores, but without values out from the range for healthy subjects (Butcher and Williams, 1992). No correlations was evidenced between HA or RD scores and MMPI 2 scores, while NS scores correlated significantly with mania scores at MMPI 2 (r=0.552; F=7.0; $P<0.01$). A trend toward the correlation, but not significant, was found between HA scores and Hamilton test scores.

3.2. Biochemical studies

3.2.1. d-fen challenge (Fig. 1)

Basal values of PRL and cortisol were in the normal range, in comparison with previous studies (PRL: ng/ml 6.7±0.6; CORT: ng/ml 10.8±1.45).

D-fen administration induced significant PRL rises ($P<0.001$, $F=40.56$, df=4,48); the average of the Areas Under the Curves (AUCs) was 174.4±47.8.

CORT showed significant responses to d-fen administration ($P<0.001$, $F=12.08$, df=4,48); the AUCs were 648.0±242 (mean±SE).

3.2.2. Clon challenge (Fig. 2)

Basal values of GH showed normal concentration before the challenge, in comparison with previous studies (GH: ng/ml 3.9±1.9). Clon administration induced significant GH rises ($P<0.001$, $F=6.87$, df=6,126). The average of the AUCs was 400.4±68.2.

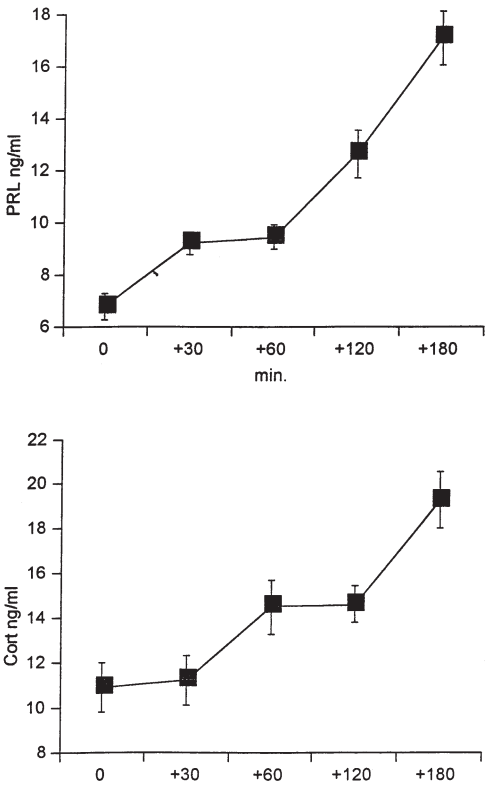

Fig. 1. Upper panel: Prolactin (PRL) response to D-fenfluramine stimulation (mean±SE) in healthy subjects (■----■). Lower panel: Cortisol (Cort) response to D-fenfluramine stimulation (mean±SE) in healthy subjects (■----■).

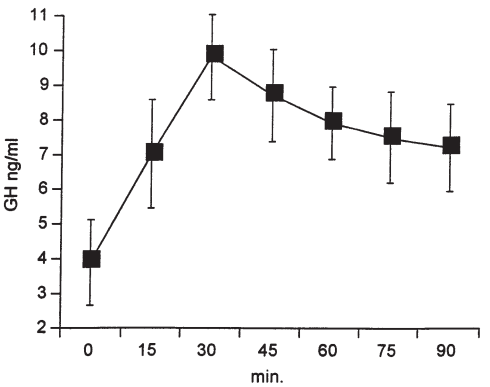

Fig. 2. Growth hormone (GH) response to clonidine stimulation (mean±SE) and in healthy subjects (■----■).

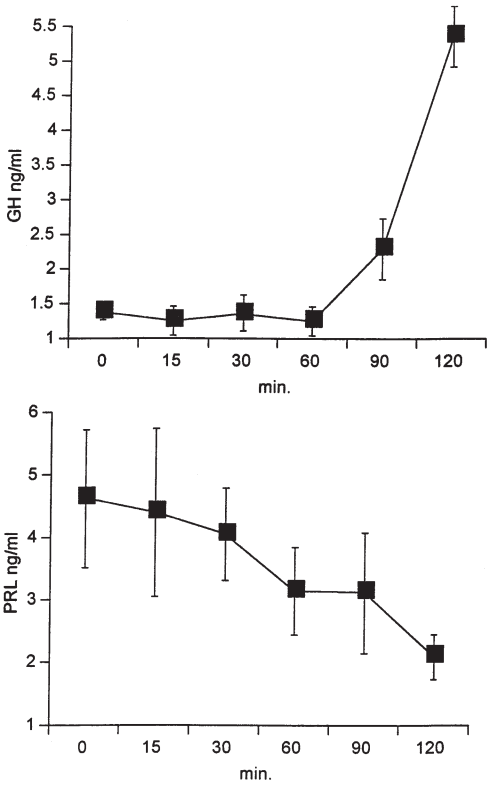

Fig. 3. Upper panel: Growth hormone (GH) response to bromocriptine stimulation (mean±SE) in healthy subjects (■----■). Lower panel: Prolactin (PRL) response to bromocriptine stimulation (mean±SE) in healthy subjects (■----■).

3.2.3. Brom challenge (Fig. 3)

Basal values of PRL were ng/ml 4.6±1.1; and basal levels of GH ng/ml 1.3±0.3.

Brom administration induced significant GH rises ($P<0.001$, $F=18.48$, df=5,105). The AUCs were 102.2±34.6.

PRL plasma levels were suppressed by brom administration with a significant decrease of the values after 90 min from Brom administration ($P<0.001$, $F=16.52$, df=1,105) AUCs were calculated as a negative number: −154.3±44.9).

3.3. Biochemical/temperament traits correlations

The correlations between hormonal responses and TPQ scores are reported in Table 1.

NS scores showed a significant direct correlation with brom-stimulated GH AUC values ($r=0.426$, $P<0.05$) (Fig. 4 upper panel) and a significant inverse correlation with brom-inhibited PRL AUC values ($r=-0.498$, $P<0.01$) (Fig. 4 lower panel). No significant correlation was observed between NS values and D-fen-stimulated PRL AUCs or CORT AUCs. GH responses to clonidine did not show any correlation with NS scores.

HA scores correlated significantly with d-fen-stimulated PRL and CORT AUCs, (PRL: $r=0.424$, $P<0.05$; CORT: $r=0.595$, $P<0.005$) (Fig. 5 upper and lower panels). The findings obtained with dopaminergic and alpha-adrenergic challenges did not evidence any significant correlation with HA scores.

RD scores correlated positively with clon-stimulated GH AUCs ($r=0.55$; $F=8.6$; $P<0.01$) (Fig. 6 upper panel) and negatively with brom-inhibited-PRL AUCs ($r=-0.439$, $P<0.05$) (Fig. 6 lower panel). No correlation was found between RD scores and the brom-stimulated GH, or PRL and CORT responses to D-denfluramine.

The scores of MMPI 2 subscales and Hamilton scores were not correlated with hormonal responses. No correlations were observed between the GH, PRL, and CORT responses to the three stimulations.

4. Discussion

Our preliminary data can offer only suggestions on the functional states of the NE, DA, and 5-HT brain systems and on the relationships between monoamine states of activity and temperament traits. However, some hypotheses can be advanced. The link between NS trait and the dopaminergic function as measured in our subjects supports the theory concerning this temperament trait and DA transporter changes (Cloninger, 1987; Noble et al., 1998). The analysis of the correlations between neurotransmitter functions and temperament traits has shown that NS scores correlate positively with D2 postsynaptic receptor sensitivity and, therefore, with decreased presynaptic DA secretion. This analysis is in agreement with most of the data in the

Table 1
Correlations between hormonal responses and TPQ scores

	GH AUCs after bromocriptine	PRL AUCs after bromocriptine	PRL AUCs after fenfluramine	Cort AUCs after fenfluramine	GH AUCs after clonidine
Novelty seeking	r=0.426; $P<0.05$	r=−0.498; $P<0.01$	ns	ns	ns
Harm avoidance	ns	ns	r=0.424; $P<0.05$	r=0.595; $P<0.01$	ns
Reward dependence	ns	r=−0.439; $P<0.05$	ns	ns	r=0.55; $P<0.01$

literature (Cloninger, 1987; Benjamin et al., 1996; Cloninger et al., 1996; Ebstein et al., 1996; Gelernter et al., 1997; Kotler et al., 1997; Ruegg et al., 1997); however, it contrasts with that of Zuckerman and Cloninger (1996) and Netter et al. (1996), which suggest that NS is underlined by DA hyper- and not hypoactivity.

A lack of association between dopamine D4 receptor gene polymorphism and personality traits has been reported by other researchers (Jonsson et al., 1998), who did not use the Cloninger TPQ for temperament assessment. Similarly, no significant associations have been observed between novelty-seeking or positive emotional experience and D4DR polymorphisms (Pogue-Geile et al., 1998). As a result, our findings, which indicate indirect evidence of a relationship between DA changes and NS trait, need to be interpreted with caution. On the other hand, bromocriptine

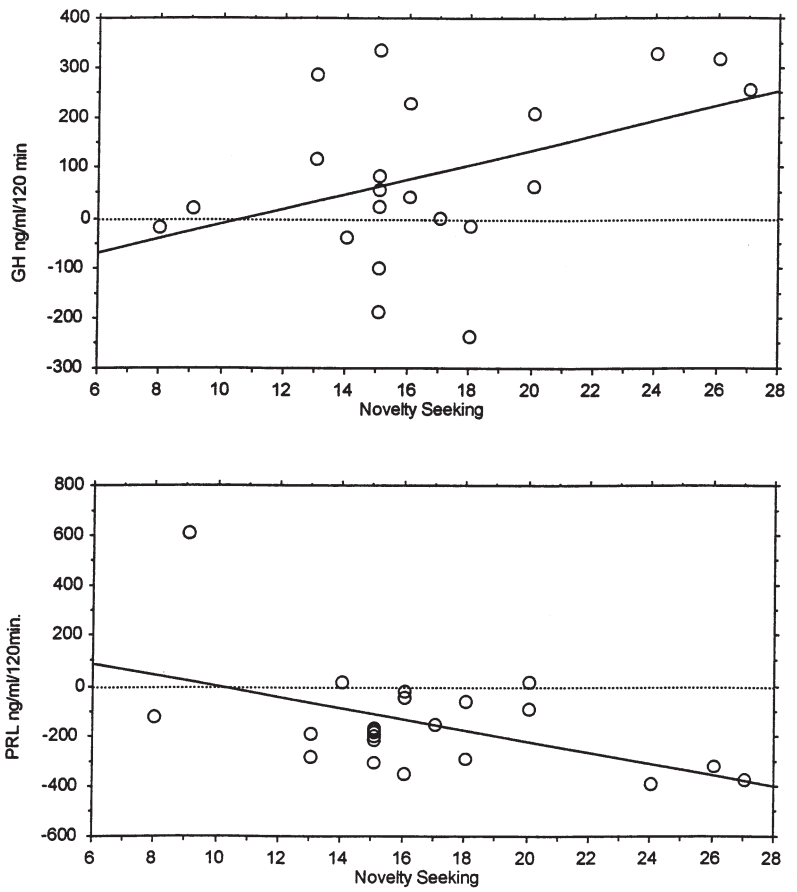

Fig. 4. Upper panel: Correlation of novelty seeking TPQ scores with GH AUCs during bromocriptine challenge in healthy subjects. Lower panel: Correlation of novelty seeking TPQ scores with PRL AUCs during bromocriptine challenge in healthy subjects.

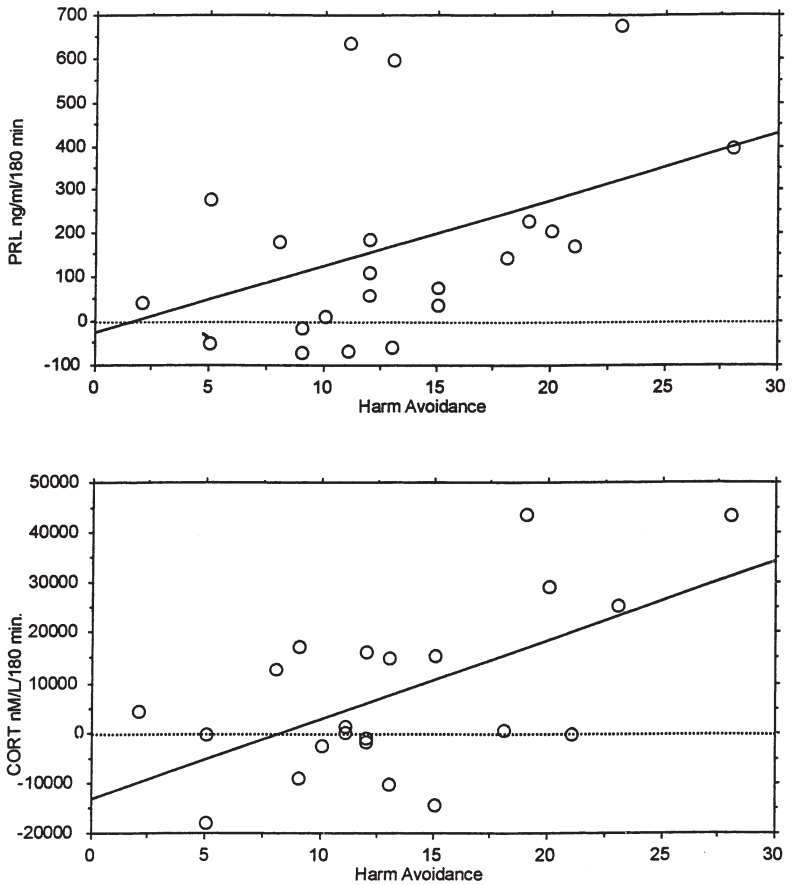

Fig. 5. Upper panel: Correlation of harm avoidance TPQ scores with PRL AUCs during D-fenfluramine challenge in healthy subjects (A). Lower panel: Correlation of harm avoidance TPQ scores with Cort AUCs during D-fenfluramine challenge in healthy subjects.

suppression of PRL secretion through the tubero-infundibular trait and bromocriptine stimulus of GH rise, with the involvement of GHRH at the hypothalamic level, may express not only post-synaptic D2 receptors' sensitivity under genetic control, but also neuroendocrine influences not directly linked with genetic factors. The expected inverse correlation between NS, sensation-seeking, and serotonergic function (Netter et al., 1996; Ruegg et al., 1997) was not found in our subjects — probably because of the small sample, as well as the likelihood that individual variability or mood changes influenced the status of 5-HT function more than temperament features did.

Harm avoidance in the healthy subjects included in our study showed a direct correlation with 5-HT function, as hypothesized by previous studies (Cloninger, 1986, 1987). However, hormonal response to D-fenfluramine is indicative of an overall hypothalamic serotonin transmission that could result from both a presynaptic

and a postsynaptic action (Maes et al., 1991; Monteleone et al., 1999). There is ample evidence that serotonin receptors are able to stimulate the secretion of hypothalamus-pituitary-adrenal axis (HPA) (Lesch et al., 1990; Lee et al., 1991; Meltzer and Maes, 1995) and that PRL responses to fenfluramine represent the influences on limbic-hypothalamic 5-HT function (Coccaro and Kavoussi, 1994). Although the present data are the expression of the neurotransmitter function in the control of hypothalamus–pituitary axes and not of the whole brain activity, the correlation between HA trait and serotonergic responses may offer strong additional support for Cloninger's theory concerning the biological mechanism of behavioral inhibition.

The trend toward a significant correlation between HA scores and Hamilton scores for depression suggests a possible relationship between this temperament trait and the development of mood disorders, based on 5-HT dysfunction (Ampollini et al., 1997). A functional polymorphism in the promoter of the human serotonin trans-

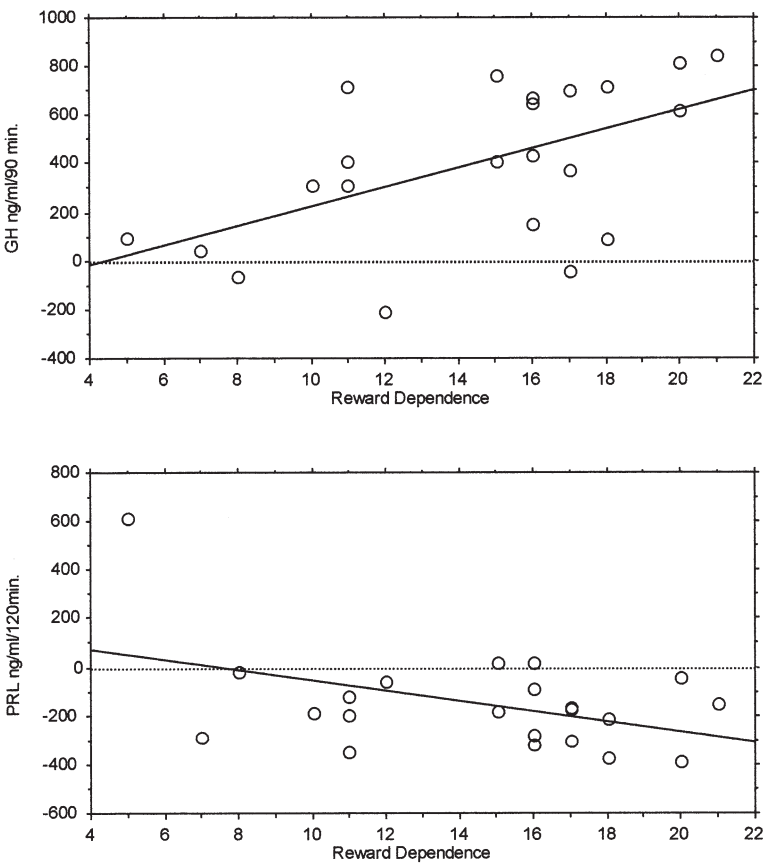

Fig. 6. Upper panel: Correlation of reward dependence TPQ scores with GH AUCs during clonidine challenge in healthy subjects. Lower panel: Correlation of reward dependence TPQ scores with PRL AUCs during bromocriptine challenge in healthy subjects.

porter gene has been found associated with two anxiety-related subdimensions of HA (anticipatory worry and fear of uncertainty) (Mazzanti et al., 1998), which could play the role of risk factors for mood disorders; the same gene has been reported to be involved in the interactions between HA and anxiety (Ricketts et al., 1998).

In our subjects, a clearly positive correlation was observed between RD and GH responses to the alpha-adrenergic test, which supports the view that reward dependent traits are associated with norepinephrine levels (Garvey et al., 1996). These results are in contrast with those of Cloninger (Cloninger et al., 1994) and Tancer (Tancer et al., 1994), who found a negative correlation between GH responses to clonidine and RD. Low GH peaks associated with high RD were found by Tancer in healthy subjects included in the study as controls, in comparison with social phobics. At this time we have no explanation for these opposing results. Blunted responses to clonidine, which would be associated with higher reward dependence scores, following Tancer et al.'s findings, were observed in attention deficit hyperactivity disorder (ADHD) (Jensen and Garfinkel, 1988) and in abstinent heroin addicts with a history of conduct disorder and ADHD (Gerra et al., 1994), but hyperactivity and antisocial personality disorder have been found in male subjects to be related with NS trait and not with RD (Hesselbrock and Hesselbrock, 1992; Johnson et al., 1997).

The significant inverse correlations between RD and the dopaminergic suppression of PRL during the bromocriptine challenge suggest that the dopaminergic function may also influence this temperament trait, a possibility which is in agreement with Kuhn (Kuhn et al., 1999), who observed an interaction between DRDA receptor polymorphism and RD.

The relationships evidenced between NS trait and dopaminergic responses, and between RD trait and alpha-adrenergic responses among healthy subjects, were not observed in a sample of patients affected by depression in a recent protocol utilizing apomorphine and clonidine challenges (Hansenne and Ansseau, 1988), suggesting that the monoamines derangement associated with depression may vanish the biological correlates of temperament traits.

In our previous studies, the positive correlations observed between NS scores and basal norepinephrine (Gerra et al., 1999), which may modulate the reward system (Cloninger et al., 1993), suggest that since a similar biochemical background seems to underlie the two personality dimensions they might actually be interrelated. The present findings, which indicate a correlation of RD scores with dopaminergic responses that are primarily linked with NS trait, appear to support the hypothesis of a NS/RD relationship.

In conclusion, our results confirm the relationships between the impairment of dopaminergic transmission and NS, and between serotonergic activity and HA. The link between RD and the monoaminergic systems function is still unclear. Caution has to be done in the interpretation of these findings: in fact, the strategies utilized in the present study, through the responses of neuroendocrine axes, provide indirect measures of parts of complex systems, that may not be evaluated as independent from one another (Asnis et al., 1992).

Further studies are needed to better investigate the relationships of temperament traits with possible biological correlates, including also gender differences evaluation.

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